WEST Search History

DATE: Wednesday, March 13, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI; PLUR=YES; OP=OR		
L7	hemachromatosis and (linkage same polymorphism$4)	0	L7
L6	L4 and (linkage same polymorphism$4)	37	L6
L5	L4 near 24d1	1	L5
L4	HH or hemachromatosis	7394	L4
L3	L1 and HH	13	L3
L2	L1 and hemachromatosis	0	L2
L1	(Ruddy) [in] or (Wolff) [in]	4364	L1

END OF SEARCH HISTORY

(FILE 'HOME' ENTERED AT 18:18:24 ON 13 MAR 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 18:18:35 ON 13 MAR 2002

L1 1726 S RUDDY D?/AU OR WOLPF R?/AU
L2 1 S L1 AND REMACHROMATOSIS
L3 17 S L1 AND HN
L4 17 DUP REM L3 (20 DUPLICATES REMOVED)
L5 9272 S HN OR HEMOCHROMOTOSIS
L6 0 S L5 (P) 24D1
L7 0 S L5 (P) 24DL
L8 304 S L5 (P) (LINKAGE OR POLYMORPHISM?)
L9 131 DUP REM L8 (173 DUPLICATES REMOVED)
L10 25 S L9 AND PD<19961523

=>

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TERMINAL (ENTER 1, 2, 3, OR ?):2


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 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2  Sep 17  IMSworld Pharmaceutical Company Directory name change
                  to PHARMASEARCH
 NEWS  3  Oct 09  Korean abstracts now included in Derwent World Patents
                  Index
 NEWS  4  Oct 09  Number of Derwent World Patents Index updates increased
 NEWS  5  Oct 15  Calculated properties now in the REGISTRY/ZREGISTRY File
 NEWS  6  Oct 22  Over 1 million reactions added to CASREACT
 NEWS  7  Oct 22  DGENE GETSIM has been improved
 NEWS  8  Oct 29  AASSD no longer available
 NEWS  9  Nov 19  New Search Capabilities  USPATFULL and USPAT2
 NEWS 10  Nov 19  TOXCENTER(SM) - new toxicology file now available on STN
 NEWS 11  Nov 29  COPPERLIT now available on STN
 NEWS 12  Nov 29  DWPI revisions to WTIS and US Provisional Numbers
 NEWS 13  Nov 30  Files VETU and VETB to have open access
 NEWS 14  Dec 10  WPINDEX/WPIDS/WPIX New and Revised Manual Codes for 2002
 NEWS 15  Dec 10  DGENE BLAST Homology Search
 NEWS 16  Dec 17  WELDASEARCH now available on STN
 NEWS 17  Dec 17  STANDARDS now available on STN
 NEWS 18  Dec 17  New fields for DPCI
 NEWS 19  Dec 19  CAS Roles modified
 NEWS 20  Dec 19  1907-1946 data and page images added to CA and CAplus
 NEWS 21  Jan 25  BLAST(R) searching in REGISTRY available in STN on the Web
 NEWS 22  Jan 25  Searching with the P indicator for Preparations
 NEWS 23  Jan 29  FSTA has been reloaded and moves to weekly updates
 NEWS 24  Feb 01  DKILIT now produced by FIZ Karlsruhe and has a new update
                  frequency
 NEWS 25  Feb 19  Access via Tymnet and SprintNet Eliminated Effective 3/31/02
 NEWS 26  Mar 08  Gene Names now available in BIOSIS

 NEWS EXPRESS   February 1 CURRENT WINDOWS VERSION IS V6.0d,
                CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
                AND CURRENT DISCOVER FILE IS DATED 05 FEBRUARY 2002
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FILE 'HOME' ENTERED AT 18:18:24 ON 13 MAR 2002

=> file medline caplus embase biosis
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FILE 'BIOSIS' ENTERED AT 18:18:35 ON 13 MAR 2002
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=> s Ruddy D?/au or Wolff R?/au
L1         1726 RUDDY D?/AU OR WOLFF R?/AU

=> s l1 and hemachromatosis
L2             1 L1 AND HEMACHROMATOSIS

=> dis l2 ibib abs

L2   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:          1999:125756  CAPLUS
DOCUMENT NUMBER:           130:178390
TITLE:                     Megabase transcript map and gene sequences in the
                           candidate hemachromatosis region of human
                           chromosome 6p21
INVENTOR(S):               Feder, John Nathan; Kronmal, Gregory Scott; Lauer,
                           Peter M.; Ruddy, David A.; Thomas, Winston;
                           Tsuchihashi, Zenta; Wolff, Roger K.
PATENT ASSIGNEE(S):        Mercator Genetics, Inc., USA
SOURCE:                    U.S., 686 pp., Cont.-in-part of U.S. Ser. No. 630,912,
                           abandoned.
                           CODEN: USXXAM
DOCUMENT TYPE:             Patent
LANGUAGE:                  English
FAMILY ACC. NUM. COUNT:    6
PATENT INFORMATION:

     PATENT NO.       KIND  DATE          APPLICATION NO.  DATE
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     US 5872237        A    19990216          US 1996-724394   19961001
     US 6025130        A    20000218          US 1996-652265   19960523
     WO 9814466        A1   19980409          WO 1997-US17688  19970930
         W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
            DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR,
            KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ,
            PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG,
            UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,
             GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
     AU 9748039        A1   19980424          AU 1997-48039    19970930
     EP 940014         A1   19991201          EP 1997-910741   19970930
         R: DE, FR, GB
     JP 2001525663     T2   20011211          JP 1998-516818   19970930
PRIORITY APPLN. INFO.:                      US 1996-630912   B2 19960404
                                            US 1996-652265   A2 19960523
                                            US 1996-632673   A2 19960416
                                            US 1996-724394   A  19961001
                                            US 1997-852495   A  19970507
                                            WO 1997-US17688  W  19970930
AB   A fine structure map of the 1 megabase region surrounding the candidate
     hemochromatosis HH gene is provided, along with 250 kb of DNA sequence and
     8 loci corresponding to candidate genes within the 1 megabase region.  The
     genes comprise a family of S butyrophilin-related sequences, 2 genes with
     structural similarity to a type I sodium phosphate transporter, and a gene
     named RoRet based on its strong similarity to the 52-kDa Ro/SSA
     autoantigen.  These loci are useful as genetic markers for further mapping
     studies.  Addnl., the 8 cDNA sequences corresponding to those loci are
     useful, for example, for the isolation of other genes in putative gene
     families, and as probes for diagnostic assays.  Addnl., the proteins
     encoded by those cDNAs are useful in the generation of antibodies for
     anal. of gene expression and in diagnostic assays, and in the purifn. of
     related proteins.
REFERENCE COUNT:         16     THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD.  ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> s l1 and hh
L3          37 L1 AND HH

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4          17 DUP REM L3 (20 DUPLICATES REMOVED)

=> dis l4 1-17 ibib abs kwic

L4   ANSWER 1 OF 17  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:    2001:482522  BIOSIS
DOCUMENT NUMBER:     PREV200100482522
TITLE:               Method for determining the presence or absence of a
                     hereditary hemochromatosis gene mutation.
AUTHOR(S):           Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.;
                     Gnirke, Andreas; Ruddy, David; Tsuchihashi,
                     Zenta; Wolff, Roger K.
                     ASSIGNEE: Bio-Rad Laboratories, Inc.
PATENT INFORMATION:  US 6228594 May 08, 2001
SOURCE:              Official Gazette of the United States Patent and Trademark
                     Office Patents, (May 8, 2001) Vol. 1246, No. 2, pp. No
                     Pagination. e-file.
                     ISSN: 0098-1133.
DOCUMENT TYPE:       Patent
LANGUAGE:            English
AB   The invention relates generally to the gene, and mutations thereto, that
     are responsible for the disease hereditary hemochromatosis (HH).
     More particularly, the invention relates to the identification, isolation,
     and cloning of the DNA sequence corresponding to the normal and mutant
     HH genes, as well as the characterization of their transcripts and
     gene products. The invention also relates to methods and the like for
     screening for HH homozygotes and further relates to HH
     diagnosis, prenatal screening and diagnosis, and therapies of HH
     disease, including gene therapeutics, protein and antibody based
     therapeutics, and small molecule therapeutics.
AU   Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas;
     Ruddy, David; Tsuchihashi, Zenta; Wolff, Roger K.
AB   The invention relates generally to the gene, and mutations thereto, that
     are responsible for the disease hereditary hemochromatosis (HH).
     More particularly, the invention relates to the identification, isolation,
     and cloning of the DNA sequence corresponding to the normal and mutant
     HH genes, as well as the characterization of their transcripts and
     gene products. The invention also relates to methods and the like for
     screening for HH homozygotes and further relates to HH
     diagnosis, prenatal screening and diagnosis, and therapies of HH
     disease, including gene therapeutics, protein and antibody based
     therapeutics, and small molecule therapeutics.

L4   ANSWER 2 OF 17  CAPLUS  COPYRIGHT 2002 ACS         DUPLICATE 1
ACCESSION NUMBER:    2000:769079  CAPLUS
DOCUMENT NUMBER:     133:318316
TITLE:               Hereditary hemochromatosis genes and their protein
                     products and mutations
INVENTOR(S):         Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.;
                     Gnirke, Andreas; Ruddy, David; Tsuchihashi,
                     Zenta; Wolff, Roger K.
PATENT ASSIGNEE(S):  Bio-Rad Laboratories, Inc., USA
SOURCE:              U.S., 108 pp., Cont.-in-part of U.S. Ser. No. 630,912,
                     abandoned.
                     CODEN: USXXAM
DOCUMENT TYPE:       Patent
LANGUAGE:            English
FAMILY ACC. NUM. COUNT:  6
PATENT INFORMATION:

     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
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     US 6140305         A     20001031      US 1997-834497   19970404
     US 5712098         A     19980127      US 1996-632673   19960416
     US 6025130         A     20000215      US 1996-652265   19960523
PRIORITY APPLN. INFO.:                      US 1996-630912   B2 19960404
                                            US 1996-632673   A2 19960416
                                            US 1996-652265   A2 19960523
AB   The invention relates generally to the gene, and mutations thereto, that
```

are responsible for the disease hereditary hemochromatosis (HH).
More particularly, the invention relates to the identification, isolation,
and cloning of the DNA sequence corresponding to the normal and mutant
HH genes, as well as the characterization of their transcripts and
gene products. The invention also related to methods and the like for
screening for HH homozygotes and further relates to HH
diagnosis, prenatal screening and diagnosis, and therapies of HH
disease, including gene therapeutics, protein and antibody based
therapeutics, and small mol. therapeutics.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IN Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas;
Ruddy, David; Teuchihashi, Zenta; **Wolff, Roger K.**
AB The invention relates generally to the gene, and mutations thereto, that
are responsible for the disease hereditary hemochromatosis (HH).
More particularly, the invention relates to the identification, isolation,
and cloning of the DNA sequence corresponding to the normal and mutant
HH genes, as well as the characterization of their transcripts and
gene products. The invention also related to methods and the like for
screening for HH homozygotes and further relates to HH
diagnosis, prenatal screening and diagnosis, and therapies of HH
disease, including gene therapeutics, protein and antibody based
therapeutics, and small mol. therapeutics.

L4 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 2
ACCESSION NUMBER: 2000:114386 CAPLUS
DOCUMENT NUMBER: 132:150279
TITLE: The gene involved in hereditary hemochromatosis and
its diagnostic and therapeutic uses
INVENTOR(S): Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.;
Gnirke, Andreas; **Ruddy, David**; Teuchihashi,
Zenta; **Wolff, Roger K.**
PATENT ASSIGNEE(S): Mercator Genetics, Inc., USA
SOURCE: U.S., 91 pp., Cont.-in-part of U.S. Ser. No. 632,673.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6025130	A	20000215	US 1996-652265	19960523
US 5712098	A	19980127	US 1996-632673	19960416
US 5872237	A	19990216	US 1996-724394	19961001
WO 9738137	A1	19971016	WO 1997-US6254	19970404
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9726701	A1	19971029	AU 1997-26701	19970404
AU 733459	B2	20010517		
EP 954602	A1	19991110	EP 1997-918642	19970404
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6140305	A	20001031	US 1997-834497	19970404
US 6228594	B1	20010508	US 2000-503444	20000214

PRIORITY APPLN. INFO.: US 1996-630912 B2 19960404
US 1996-632673 A2 19960416
US 1996-652265 A2 19960523
WO 1997-US6254 W 19970404

AB The HH gene that is mutated in the disease hereditary
hemochromatosis (HH) is cloned and wild-type and mutant alleles
assocd. with the disease are characterized. In addn., the gene products
of these alleles are characterized. The invention also relates to methods
and the like for screening for HH homozygotes for diagnosis,
prenatal screening and diagnosis, treatment of the disease, including gene
therapy, protein and antibody based therapy, and small mol. therapeutics.
The gene product is similar to an MHC mol. but the gene, which maps close
to the MHC cluster on chromosome 6p, does not show the polymorphism
typical of member of the MHC family.
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
IN Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas;
Ruddy, David; Teuchihashi, Zenta; **Wolff, Roger K.**
AB The HH gene that is mutated in the disease hereditary
hemochromatosis (HH) is cloned and wild-type and mutant alleles
assocd. with the disease are characterized. In addn., the gene products
of these alleles are characterized. The invention also relates to methods
and the like for screening for HH homozygotes for diagnosis,
prenatal screening and diagnosis, treatment of the disease, including gene
therapy, protein and antibody based therapy, and small mol. therapeutics.
The gene product is similar to an MHC mol. but the gene, which maps close
to the MHC cluster on chromosome 6p, does not show the polymorphism
typical of member of the MHC family.
IT Gene, animal
RL: BOC (Biological occurence); PRP (Properties); THU (Therapeutic use);
BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(HH; gene involved in hereditary hemochromatosis and its
diagnostic and therapeutic uses)
IT Proteins, specific or class
RL: BPR (Biological process); PRP (Properties); THU (Therapeutic use);
BIOL (Biological study); PROC (Process); USES (Uses)
(gene HR, in iron absorption; gene involved in hereditary
hemochromatosis and its diagnostic and therapeutic uses)

L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:125756 CAPLUS
DOCUMENT NUMBER: 130:178390
TITLE: Megabase transcript map and gene sequences in the
candidate hemachromatosis region of human chromosome
6p21
INVENTOR(S): Feder, John Nathan; Kronmal, Gregory Scott; Lauer,
Peter M.; **Ruddy, David A.**; Thomas, Winston;
Teuchihashi, Zenta; **Wolff, Roger K.**
PATENT ASSIGNEE(S): Mercator Genetics, Inc., USA
SOURCE: U.S., 686 pp., Cont.-in-part of U.S. Ser. No. 630,912,
abandoned.
CODEN: USXXAM

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5872237	A	19990216	US 1996-724394	19961001
US 6025130	A	20000215	US 1996-652265	19960523
WO 9814466	A1	19980409	WO 1997-US17658	19970930
W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG			
AU 9748039	A1	19980424	AU 1997-48039	19970930
EP 960114	A1	19991201	EP 1997-910741	19970930
R:	DE, FR, GB			
JP 2001525663	T2	20011211	JP 1998-516815	19970930

PRIORITY APPLN. INFO.: US 1996-630912 B2 19960404
US 1996-652265 A2 19960523
US 1996-652673 A2 19960416
US 1996-724394 A 19961001
US 1997-852695 A 19970507
WO 1997-US17658 W 19970930

AB A fine structure map of the 1 megabase region surrounding the candidate hemochromatosis **HH** gene is provided, along with 250 kb of DNA sequence and 8 loci corresponding to candidate genes within the 1 megabase region. The genes comprise a family of 5 butyrophilin-related sequences, 2 genes with structural similarity to a type I sodium phosphate transporter, and a gene named RoRet based on its strong similarity to the 52-kDa Ro/SSA autoantigen. These loci are useful as genetic markers for further mapping studies. Addnl., the 8 cDNA sequences corresponding to those loci are useful, for example, for the isolation of other genes in putative gene families, and as probes for diagnostic assays. Addnl., the proteins encoded by those cDNAs are useful in the generation of antibodies for anal. of gene expression and in diagnostic assays, and in the purifn. of related proteins.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IN Feder, John Nathan; Kronmal, Gregory Scott; Lauer, Peter M.; **Ruddy, David A.**; Thomas, Winston; Tsuchihashi, Zenta; **Wolff, Roger K.**

AB A fine structure map of the 1 megabase region surrounding the candidate hemochromatosis **HH** gene is provided, along with 250 kb of DNA sequence and 8 loci corresponding to candidate genes within the 1 megabase region. The genes comprise a family of 5 butyrophilin-related sequences, 2 genes with structural similarity to a type I sodium phosphate transporter, and a gene named RoRet based on its strong similarity to the 52-kDa Ro/SSA autoantigen. These loci are useful as genetic markers for further mapping studies. Addnl., the 8 cDNA sequences corresponding to those loci are useful, for example, for the isolation of other genes in putative gene families, and as probes for diagnostic assays. Addnl., the proteins encoded by those cDNAs are useful in the generation of antibodies for anal. of gene expression and in diagnostic assays, and in the purifn. of related proteins.

L4 ANSWER 5 OF 17 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999091925 MEDLINE
DOCUMENT NUMBER: 99091925 PubMed ID: 9873093
TITLE: Hereditary hemochromatosis in liver transplantation.
AUTHOR: Fiel M I; Schiano T D; Bodenheimer H C; Thung S N; King T W; Varma C R; Miller C M; Brunt E M; Starnes S; Prass C; **Wolff R K**; Bacon B R
CORPORATE SOURCE: Department of Medicine, The Mount Sinai School of Medicine, New York, NY, USA.
SOURCE: LIVER TRANSPLANTATION AND SURGERY, (1999 Jan) 5 (1) 50-6.
Journal code: CX3; 9502504. ISSN: 1074-3022.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199902
ENTRY DATE: Entered STN: 19990223
Last Updated on STN: 19990223
Entered Medline: 19990211

AB A candidate gene, HFE, was recently described in patients with hereditary hemochromatosis (**HH**) and found to contain a missense mutation leading to a cysteine to tyrosine substitution (C282Y). A second mutation, H63D, was also found in the gene. This study was undertaken to determine the HFE genotype in liver transplant recipients clinically diagnosed with **HH** and those incidentally found to have increased iron deposition in their explanted livers and to evaluate whether biochemical or histological hepatic iron indices (HIIs) correlated with homozygosity for the C282Y mutation. We identified 15 patients clinically diagnosed with various liver disorders other than **HH** who had increased liver iron deposits among 918 adult patients who underwent liver transplantation from 1988 to 1995. Four additional patients were clinically diagnosed as having **HH**. Archival explant liver tissue was evaluated for the histological HII according to the method of Deugnier et al, in which an index greater than 0.15 suggests homozygosity for **HH**. The HII was computed according to established methods, with a value greater than 1.9 suggesting homozygosity for **HH**. A portion of liver tissue was subjected to DNA genotyping using polymerase chain reaction-amplified products. Two of 4 patients with clinically suspected **HH** were homozygous for C282Y, and 2 patients had neither mutation. One of the 15 patients not suspected to have **HH** was a C282Y homozygote, 1 was a C282Y heterozygote, 6 were H63D heterozygotes, and 7 had neither mutation. The histological HII was consistent with **HH** in 13 patients, whereas the HII was consistent with **HH** in 6 patients. Thus, in patients with end-stage liver disease, despite fulfilling the established clinical criteria for **HH** using biochemical and histological parameters, only a minority of patients were homozygous for the C282Y mutation. Hepatic iron overload may result from other causes, and in end-stage liver disease, an elevated HII may not accurately predict **HH**. Other factors that either control or lead to iron absorption may explain iron overload in these patients.

AU. - C; Thung S N; King T W; Varma C R; Miller C M; Brunt E M; Starnes S; Prass C; **Wolff R K**; Bacon B R

AB A candidate gene, HFE, was recently described in patients with hereditary

hemochromatosis (HH) and found to contain a missense mutation leading to a cysteine to tyrosine substitution (C282Y). A second mutation, H63D, was ... found in the gene. This study was undertaken to determine the HFE genotype in liver transplant recipients clinically diagnosed with HH and those incidentally found to have increased iron deposition in their explanted livers and to evaluate whether biochemical or histological ... (HIIs) correlated with homozygosity for the C282Y mutation. We identified 15 patients clinically diagnosed with various liver disorders other than HH who had increased liver iron deposits among 918 adult patients who underwent liver transplantation from 1982 to 1995. Four additional patients were clinically diagnosed as having HH. Archival explant liver tissue was evaluated for the histological HII according to the method of Deugnier et al, in which an index greater than 0.15 suggests homozygosity for HH. The HII was computed according to established methods, with a value greater than 1.9 suggesting homozygosity for HH. A portion of liver tissue was subjected to DNA genotyping using polymerase chain reaction-amplified products. Two of 4 patients with clinically suspected HH were homozygous for C282Y, and 2 patients had neither mutation. One of the 15 patients not suspected to have HH was a C282Y homozygote, 1 was a C282Y heterozygote, 6 were H63D heterozygotes, and 7 had neither mutation. The histological HII was consistent with HH in 13 patients, whereas the HII was consistent with HH in 6 patients. Thus, in patients with end-stage liver disease, despite fulfilling the established clinical criteria for HH using biochemical and histological parameters, only a minority of patients were homozygous for the C282Y mutation. Hepatic iron overload may result from other causes, and in end-stage liver disease, an elevated HII may not accurately predict HH. Other factors that either control or lead to iron absorption may explain iron overload in these patients.

L4 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:75992 CAPLUS
DOCUMENT NUMBER: 128:150362
TITLE: Hereditary hemochromatosis diagnostic genetic markers and diagnostic methods
INVENTOR(S): Teuchihashi, Zenta; Gnirke, Andreas; Thomas, Winston J.; Drayna, Dennis T.; **Ruddy, David**; **Wolff, Roger K.**; Feder, John N.
PATENT ASSIGNEE(S): Mercator Genetics, USA
SOURCE: U.S., 17 pp. Cont.-in-part of U.S. Ser. No. 630,912, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5712098	A	19980127	US 1996-632673	19960416
US 6025130	A	20000215	US 1996-652265	19960523
WO 9738137	A1	19971016	WO 1997-US6254	19970404
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GH, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9726701	A1	19971029	AU 1997-26701	19970404
AU 733459	B2	20010517		
EP 954602	A1	19991110	EP 1997-918642	19970404
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6140305	A	20001031	US 1997-834497	19970404
US 6228594	B1	20010508	US 2000-503444	20000214

PRIORITY APPLN. INFO.: US 1996-630912 A2 19960404
US 1996-632673 A2 19960416
US 1996-652265 A2 19960523
WO 1997-US6254 W 19970404

AB A single base-pair polymorphism involving a mutation from Guanine (G), in individuals unaffected by the hereditary hemochromatosis (HH) gene defect, to Adenine (A), in individuals affected by the HH gene defect is disclosed. The presence or absence of the polymorphic allele is highly predictive of whether an individual is at risk from HH: the polymorphism is present in 82% of affected individuals and only 4% of a random population screen. Methods of diagnosis, markers, and PCR primers are disclosed.

IN Teuchihashi, Zenta; Gnirke, Andreas; Thomas, Winston J.; Drayna, Dennis T.; **Ruddy, David**; **Wolff, Roger K.**; Feder, John N.

AB A single base-pair polymorphism involving a mutation from Guanine (G), in individuals unaffected by the hereditary hemochromatosis (HH) gene defect, to Adenine (A), in individuals affected by the HH gene defect is disclosed. The presence or absence of the polymorphic allele is highly predictive of whether an individual is at risk from HH: the polymorphism is present in 82% of affected individuals and only 4% of a random population screen. Methods of diagnosis, markers, and PCR primers are disclosed.

L4 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:31106 CAPLUS
DOCUMENT NUMBER: 128:124494
TITLE: Hereditary hemochromatosis gene point mutations as markers and PCR primers for disease diagnosis
INVENTOR(S): Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; Kimmel, Bruce E.; Thomas, Winston J.; **Wolff, Roger K.**
PATENT ASSIGNEE(S): Mercator Genetics, Inc., USA
SOURCE: U.S., 67 pp. Cont.-in-part of U.S. Ser. No. 559,302.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5705343	A	19980106	US 1996-599252	19960209
US 5753438	A	19980519	US 1995-436074	19950508
WO 9635802	A1	19961114	WO 1996-US6352	19960506
W: AU, CA				

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
AU 9657282 A1 19961129 AU 1996-57282 19960506
CA 2220293 AA 19961114 CA 1996-2220293 19960508
WO 9635803 A1 19961114 WO 1996-US6583 19960508
W: AU, CA
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
ZA 9603639 A 19961119 ZA 1996-3639 19960508
AU 9658559 A1 19961129 AU 1996-58559 19960508
AU 722885 B2 20000810
EP 827550 A1 19980311 EP 1996-920167 19960508
R: AT, BE, DE, DK, ES, FR, GB, IT, NL, SE, PT, IE
PRIORITY APPLN. INFO.: US 1995-436074 A2 19950508
US 1995-559302 A2 19951115
US 1996-599252 A 19960209
WO 1996-US6352 W 19960506
WO 1996-US6583 W 19960508

AB New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes contg. this mutation in their genomic DNA. Oligonucleotide primers for PCR or OLA (oligonucleotide ligation assay) are described for HH diagnosis and to identify a potential reduced responsiveness of a subject to interferon treatment for hepatitis C.

IN Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; Kimmel, Bruce E.; Thomas, Winston J.; **Wolff, Roger K.**

AB New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes contg. this mutation in their genomic DNA. Oligonucleotide primers for PCR or OLA (oligonucleotide ligation assay) are described for HH diagnosis and to identify a potential reduced responsiveness of a subject to interferon treatment for hepatitis C.

L4 ANSWER 8 OF 17 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998151540 MEDLINE
DOCUMENT NUMBER: 98151540 PubMed ID: 9482913
TITLE: HFE gene knockout produces mouse model of hereditary hemochromatosis.
COMMENT: Comment in: Proc Natl Acad Sci U S A. 1998 Mar 3;95(5):2033-4
AUTHOR: Zhou X Y; Tomatsu S; Fleming R E; Parkkila S; Waheed A; Jiang J; Fei Y; Brunt E M; **Ruddy D A**; Prass C E; Schatzman R C; O'Neill R; Britton R S; Bacon B R; Sly W S
CORPORATE SOURCE: Edward A. Doisy Department of Biochemistry and Molecular Biology, St. Louis University School of Medicine, 1402 South Grand Boulevard, St. Louis, MO 63104, USA.
CONTRACT NUMBER: DK40163 (NIDDK)
DK41816 (NIDDK)
GM34182 (NIGMS)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Mar 3) 95 (5) 2492-7. Journal code: PV3; 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980409

AB Hereditary hemochromatosis (HH) is a common autosomal recessive disease characterized by increased iron absorption and progressive iron storage that results in damage to major organs in the body. Recently, a candidate gene for HH called HFE encoding a major histocompatibility complex class I-like protein was identified by positional cloning. Nearly 90% of Caucasian HH patients have been found to be homozygous for the same mutation (C282Y) in the HFE gene. To test the hypothesis that the HFE gene is involved in regulation of iron homeostasis, we studied the effects of a targeted disruption of the murine homologue of the HFE gene. The HFE-deficient mice showed profound differences in parameters of iron homeostasis. Even on a standard diet, by 10 weeks of age, fasting transferrin saturation was significantly elevated compared with normal littermates (96 +/- 5% vs. 77 +/- 3%, P < 0.007), and hepatic iron concentration was 8-fold higher than that of wild-type littermates (2,071 +/- 450 vs. 255 +/- 23 microg/g dry wt., P < 0.002). Stainable hepatic iron in the HFE mutant mice was predominantly in hepatocytes in a periportal distribution. Iron concentrations in spleen, heart, and kidney were not significantly different. Erythroid parameters were normal, indicating that the anemia did not contribute to the increased iron storage. This study shows that the HFE protein is involved in the regulation of iron homeostasis and that mutations in this gene are responsible for HH. The knockout mouse model of HH will facilitate investigation into the pathogenesis of increased iron accumulation in HH and provide opportunities to evaluate therapeutic strategies for prevention or correction of iron overload.

AU Zhou X Y; Tomatsu S; Fleming R E; Parkkila S; Waheed A; Jiang J; Fei Y; Brunt E M; **Ruddy D A**; Prass C E; Schatzman R C; O'Neill R; Britton R S; Bacon B R; Sly W S

AB Hereditary hemochromatosis (HH) is a common autosomal recessive disease characterized by increased iron absorption and progressive iron storage that results in damage to major organs in the body. Recently, a candidate gene for HH called HFE encoding a major histocompatibility complex class I-like protein was identified by positional cloning. Nearly 90% of Caucasian HH patients have been found to be homozygous for the same mutation (C282Y) in the HFE gene. To test the hypothesis. . . . the HFE protein is involved in the regulation of iron homeostasis and that mutations in this gene are responsible for HH. The knockout mouse model of HH will facilitate investigation into the pathogenesis of increased iron accumulation in HH and provide opportunities to evaluate therapeutic strategies for prevention or correction of iron overload.

L4 ANSWER 9 OF 17 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998179138 MEDLINE
DOCUMENT NUMBER: 98179138 PubMed ID: 9510559
TITLE: Major histocompatibility complex class I associations in iron overload: evidence for a new link between the HFE H63D mutation, HLA-A29, and non-classical forms of hemochromatosis.
AUTHOR: Porto G; Alves H; Rodrigues P; Cabeda J M; Portal C; Ruivo A; Justica B; **Wolff R**; De Sousa M

CORPORATE SOURCE: Santo Antonio General Hospital, Largo do Prof. Abel Salazar, no.1, P-4050 Porto, Portugal.
SOURCE: IMMUNOGENETICS, (1998 Apr) 47 (5) 404-10. Journal code: G14. ISSN: 0093-7711.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001234

AB The present study is an analysis of the frequencies of HFE mutations in patients with different forms of iron overload compared with the frequencies found in healthy subjects from the same region. The frequencies of HLA-A and -B antigens and HLA haplotypes were also analysed in the same subjects. The study population included: 71 healthy individuals; 39 genetically and clinically well-characterized patients with genetic hemochromatosis (HH); and 25 patients with non-classical forms of iron overload (NCH), excluding secondary hemochromatosis. All subjects were HLA-typed and HFE-genotyped by the oligonucleotide ligation assay (OLA). The gene frequencies found for the C282Y and H63D mutations of HFE were respectively: 0.03 and 0.23 in healthy individuals, 0.86 and 0.04 in HH patients, and 0.08 and 0.48 in NCH patients. An expected significant association between HH and HLA-A3 was observed, which was found to be in linkage disequilibrium with the C282Y mutation. A new association was seen, however, between HLA-A29 and NCH, in linkage disequilibrium with the H63D mutation. Again as expected, the HLA-B antigen B7 was associated with HH in linkage disequilibrium with HLA-A3. In addition, the HLA-B antigen B44 was found to be associated with NCH but not in linkage disequilibrium with either A29 or the H63D mutation. In conclusion, a new association of the HFE H63D mutation with forms of hemochromatosis other than HH and a new association between the HLA phenotype A29 and the HFE H63D mutation were found in the same patients. These findings reinforce evidence for the involvement of the major histocompatibility class I in iron metabolism, supporting the notion of a physiological role for the immunological system in the regulation of iron load.

AU Porto G; Alves H; Rodrigues P; Cabeda J M; Portal C; Ruivo A; Justica B; **Wolff R**; De Sousa M

AB . . . in the same subjects. The study population included: 71 healthy individuals; 39 genetically and clinically well-characterized patients with genetic hemochromatosis (HH); and 25 patients with non-classical forms of iron overload (NCH), excluding secondary hemochromatosis. All subjects were HLA-typed and HFE-genotyped by . . . for the C282Y and H63D mutations of HFE were respectively: 0.03 and 0.23 in healthy individuals, 0.86 and 0.04 in HH patients, and 0.08 and 0.48 in NCH patients. An expected significant association between HH and HLA-A3 was observed, which was found to be in linkage disequilibrium with the C282Y mutation. A new association was . . . HLA-A29 and NCH, in linkage disequilibrium with the H63D mutation. Again as expected, the HLA-B antigen B7 was associated with HH in linkage disequilibrium with HLA-A3. In addition, the HLA-B antigen B44 was found to be associated with NCH but not . . . or the H63D mutation. In conclusion, a new association of the HFE H63D mutation with forms of hemochromatosis other than HH and a new association between the HLA phenotype A29 and the HFE H63D mutation were found in the same patients. . . .

L4 ANSWER 10 OF 17 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999187982 MEDLINE
DOCUMENT NUMBER: 99187982 PubMed ID: 10087990
TITLE: Transferrin receptor mutation analysis in hereditary hemochromatosis patients.
AUTHOR: Tsuchihashi Z; Hansen S L; Quintana L; Kronmal G S; Mapa F A; Feder J N; **Wolff R K**
CORPORATE SOURCE: Progenitor, Inc., Menlo Park, CA 94025, USA.. zentas@progenitor.com
SOURCE: BLOOD CELLS, MOLECULES, AND DISEASES, (1998 Sep) 24 (3) 317-21. Journal code: BSA; 9509932. ISSN: 1079-9796.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990503

AB The Cys282-->Tyr mutation in the HFE gene is carried by the majority of hereditary hemochromatosis patient chromosomes, yet some patients do not seem to harbor any mutation in this gene. This suggests a possibility that these patients may have a mutation in other genes in the same pathway as HFE. We analyzed the cDNA sequences of transferrin receptor (TFR), which was recently shown to interact with HFE, in twenty-one hereditary hemochromatosis patients including sixteen individuals who did not carry a Cys282-->Tyr mutation. A nucleotide substitution (424A-->G), which resulted in the Ser142-->Gly amino acid substitution, was the only amino acid polymorphism detected in the open reading frame of the TFR gene in these patients. This amino acid substitution was a rather common polymorphism in the general population (49%) and its frequency did not significantly differ in the hereditary hemochromatosis (HH) patients regardless of the HFE genotype. Thus, amino acid changes in the TFR gene do not appear to play a role in HH even when the patients do not have a HFE mutation. However, this study does not rule out the possibility of the involvement of mutations in non-coding regions.

AU Tsuchihashi Z; Hansen S L; Quintana L; Kronmal G S; Mapa F A; Feder J N; **Wolff R K**

AB . . . a rather common polymorphism in the general population (49%) and its frequency did not significantly differ in the hereditary hemochromatosis (HH) patients regardless of the HFE genotype. Thus, amino acid changes in the TFR gene do not appear to play a role in HH even when the patients do not have a HFE mutation. However, this study does not rule out the possibility of. . .

L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:684528 CAPLUS
DOCUMENT NUMBER: 127:355966
TITLE: Cloning and sequencing of hereditary hemochromatosis gene with therapeutic and diagnostic approaches for disease treatment
INVENTOR(S): Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; **Ruddy, David**; Tsuchihashi,

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                    Zenta; Wolff, Roger K.
PATENT ASSIGNEE(S):  Mercator Genetics, Inc., USA; Thomas, Winston J.;
                    Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas;
                    Ruddy, David; Tsuchihashi, Zenta; Wolff, Roger K.
SOURCE:             PCT Int. Appl., 114 pp.
                    CODEN: PIXXD2
DOCUMENT TYPE:      Patent
LANGUAGE:           English
FAMILY ACC. NUM. COUNT:  6
PATENT INFORMATION:

     PATENT NO.          KIND  DATE        APPLICATION NO.  DATE
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     WO 9738137          A1    19971016    WO 1997-US6254   19970404
          W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ,
             LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,
             PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ,
             US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
          RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB,
             GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN,
             ML, MR, NE, SN, TD, TG
     US 5732098          A     19980327    US 1996-632673   19960404
     US 6025130          A     20000215    US 1996-652265   19960523
     AU 9726701          A1    19971029    AU 1997-26701    19970404
     AU 733459           B2    20010517
     EP 954602           A1    19991110    EP 1997-918642   19970404
          R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
PRIORITY APPLN. INFO.:                     US 1996-630912   A2 19960404
                                           US 1996-632673   A2 19960404
                                           US 1996-652265   A2 19960523
                                           WO 1997-US6254   W  19970404
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AB The identification, isolation, and cloning of the DNA sequence, transcripts and gene products corresponding to the gene and mutations that are responsible for the disease hereditary hemochromatosis (HH) is presented. Methods are presented for PCR screening for HH homozygotes and further relates to HH diagnosis, prenatal screening and diagnosis, and therapies of HH disease, including gene therapeutics, protein and antibody based therapeutics, and small mol. therapeutics.


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IN  Thomas, Winston J.; Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas;
    Ruddy, David; Tsuchihashi, Zenta; Wolff, Roger K.
```


AB The identification, isolation, and cloning of the DNA sequence, transcripts and gene products corresponding to the gene and mutations that are responsible for the disease hereditary hemochromatosis (HH) is presented. Methods are presented for PCR screening for HH homozygotes and further relates to HH diagnosis, prenatal screening and diagnosis, and therapies of HH disease, including gene therapeutics, protein and antibody based therapeutics, and small mol. therapeutics.


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IT  Disease models
        (disease model for HH disease with mutant or knocked-out
        gene; cloning and sequencing of hereditary hemochromatosis gene with
        therapeutic and diagnostic approaches for disease treatment)
IT  Epitopes
        (specific for hemochromatosis gene HH protein epitope;
        cloning and sequencing of hereditary hemochromatosis gene with
        therapeutic and diagnostic approaches for disease treatment)
IT  Monoclonal antibodies
    RL: ARG (Analytical reagent use); BSU (Biological study, unclassified);
    THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study);
    USES (Uses)
        (specific for hemochromatosis gene HH protein epitope;
        cloning and sequencing of hereditary hemochromatosis gene with
        therapeutic and diagnostic approaches for disease treatment)
IT  Genes (animal)
    RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
    (Biological study); USES (Uses)
        (targeting, disease model for HH disease with mutant or
        knocked-out gene; cloning and sequencing of hereditary hemochromatosis
        gene with therapeutic and diagnostic approaches for disease treatment)

L4  ANSWER 12 OF 17     MEDLINE                          DUPLICATE 7
ACCESSION NUMBER:   97306296      MEDLINE
DOCUMENT NUMBER:    97306296      PubMed ID: 9162021
TITLE:              The hemochromatosis founder mutation in HLA-H disrupts
                    beta2-microglobulin interaction and cell surface
                    expression.
AUTHOR:             Feder J N; Tsuchihashi Z; Irrinki A; Lee V K; Mapa F A;
                    Morikang E; Prass C E; Starnes S M; Wolff R K;
                    Parkkila S; Sly W S; Schatzman R C
CORPORATE SOURCE:   Mercator Genetics, Inc., Menlo Park, California 94025, USA.
SOURCE:             JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 30) 272 (22)
                    14025-8.
                    Journal code: HIV; 2985121R. ISSN: 0021-9258.
PUB. COUNTRY:       United States
                    Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Priority Journals
ENTRY MONTH:        199706
ENTRY DATE:         Entered STN: 19970716
                    Last Updated on STN: 19970716
                    Entered Medline: 19970627
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AB We recently reported the positional cloning of a candidate gene for hereditary hemochromatosis (HH), called HLA-H, which is a novel member of the major histocompatibility complex class I family. A mutation in this gene, cysteine 282 --> tyrosine (C282Y), was found to be present in 83% of HH patient DNAs, while a second variant, histidine 63 --> aspartate (H63D), was enriched in patients heterozygous for C282Y. The functional relevance of either mutation has not been described. Co-immunoprecipitation studies of cell lysates from human embryonic kidney cells transfected with wild-type or mutant HLA-H cDNA demonstrate that wild-type HLA-H binds beta2-microglobulin and that the C282Y mutation, but not the H63D mutation, completely abrogates this interaction. Immunofluorescence labeling and subcellular fractionations demonstrate that while the wild-type and H63D HLA-H proteins are expressed on the cell surface, the C282Y mutant protein is localized exclusively intracellularly. This report describes the first functional significance of the C282Y mutation by suggesting that an abnormality in protein trafficking and/or cell-surface expression of HLA-H leads to HH disease.


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AU  . . J N; Tsuchihashi Z; Irrinki A; Lee V K; Mapa F A; Morikang E; Prass
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C E; Starnes S M; **Wolff R K**; Parkkila S; Sly W S; Schatzman R C

AB We recently reported the positional cloning of a candidate gene for hereditary hemochromatosis (HH), called HLA-H, which is a novel member of the major histocompatibility complex class I family. A mutation in this gene, cysteine 282 --> tyrosine (C282Y), was found to be present in 83% of HH patient DNAs, while a second variant, histidine 63 --> aspartate (H63D), was enriched in patients heterozygous for C282Y. The functional . . . significance of the C282Y mutation by suggesting that an abnormality in protein trafficking and/or cell-surface expression of HLA-H leads to HH disease.

L4 ANSWER 13 OF 17 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 97294057 MEDLINE
DOCUMENT NUMBER: 97294057 PubMed ID: 9149941
TITLE: A 1.1-Mb transcript map of the hereditary hemochromatosis locus.
AUTHOR: **Ruddy D A**; Kronmal G S; Lee V K; Mintier G A; Quintana L; Domingo R Jr; Meyer N C; Irrinki A; McClelland E E; Pullan A; Mapa P A; Moore T; Thomas W; Loeb D B; Harmon C; Tsuchihashi Z; **Wolff R K**; Schatzman R C; **Feder J N**
CORPORATE SOURCE: Mercator Genetics, Menlo Park, California 94025, USA.
SOURCE: GENOME RESEARCH, (1997 May) 7 (5) 441-56.
Journal code: CES; 9518021. ISSN: 1088-9051.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U60319; GENBANK-U90543; GENBANK-U90544; GENBANK-U90545; GENBANK-U90546; GENBANK-U90547; GENBANK-U90548; GENBANK-U90550; GENBANK-U90551; GENBANK-U90552; GENBANK-U91328
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 19970813
Last Updated on STN: 19970813
Entered Medline: 19970804

AB In the process of positionally cloning a candidate gene responsible for hereditary hemochromatosis (HH), we constructed a 1.1-Mb transcript map of the region of human chromosome 6p that lies 4.5 Mb telomeric to HLA-A. A combination of three gene-finding techniques, direct cDNA selection, exon trapping, and sample sequencing, were used initially for a saturation screening of the 1.1-Mb region for expressed sequence fragments. As genetic analysis further narrowed the HH candidate locus, we sequenced completely 0.25 Mb of genomic DNA as a final measure to identify all genes. Besides the novel MHC class 1-like HH candidate gene HLA-H, we identified a family of five butyrophilin-related sequences, two genes with structural similarity to a type 1 sodium phosphate transporter, 12 novel histone genes, and a gene we named RoRet based on its strong similarity to the 52-kD Ro/SSA lupus and Sjogren's syndrome auto-antigen and the RET finger protein. Several members of the butyrophilin family and the RoRet gene share an exon of common evolutionary origin called B30.2. The B30.2 exon was originally isolated from the HLA class 1 region, yet has apparently "shuffled" into several genes along the chromosome telomeric to the MHC. The conservation of the B30.2 exon in several novel genes and the previously described amino acid homology of HLA-H to MHC class 1 molecules provide further support that this gene-rich region of 6p21.3 is related to the MHC. Finally, we performed an analysis of the four approaches for gene finding and conclude that direct selection provides the most effective probes for cDNA screening, and that as much as 30% of ESTs in this 1.1-Mb region may be derived from noncoding genomic DNA.

AU **Ruddy D A**; Kronmal G S; Lee V K; Mintier G A; Quintana L; Domingo R Jr; Meyer N C; Irrinki . . . A; McClelland E E; Pullan A; Mapa P A; Moore T; Thomas W; Loeb D B; Harmon C; Tsuchihashi Z; **Wolff R K**; Schatzman R C; **Feder J N**

AB In the process of positionally cloning a candidate gene responsible for hereditary hemochromatosis (HH), we constructed a 1.1-Mb transcript map of the region of human chromosome 6p that lies 4.5 Mb telomeric to HLA-A. . . . used initially for a saturation screening of the 1.1-Mb region for expressed sequence fragments. As genetic analysis further narrowed the HH candidate locus, we sequenced completely 0.25 Mb of genomic DNA as a final measure to identify all genes. Besides the novel MHC class 1-like HH candidate gene HLA-H, we identified a family of five butyrophilin-related sequences, two genes with structural similarity to a type 1. . .

L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:41861 CAPLUS
DOCUMENT NUMBER: 126:55929
TITLE: Hereditary hemochromatosis gene point mutations as markers and PCR primers for disease diagnosis
INVENTOR(S): Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; Kimmel, Bruce E.; Thomas, Winston J.; **Wolff, Roger K.**
PATENT ASSIGNEE(S): Mercator Genetics, Inc., USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9635803	A1	19961114	WO 1996-US6583	19960508
W: AU, CA				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5753438	A	19980519	US 1995-436074	19950508
US 5705343	A	19980106	US 1996-559252	19960209
ZA 9603639	A	19961119	ZA 1996-3639	19960508
AU 9658559	A1	19961129	AU 1996-58559	19960508
AU 722885	B2	20000810		
EP 827550	A1	19980311	EP 1996-920167	19960508
R: AT, BE, DE, DK, ES, FR, GB, IT, NL, SE, PT, IE				

PRIORITY APPLN. INFO.: US 1995-436074 A 19950508
US 1995-559302 A 19951115
US 1996-559252 A 19960209
WO 1996-US6583 W 19960508

AB New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes contg. this mutation in their genomic DNA. PCR primers are described for HH diagnosis.

IN Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; Kimmel, Bruce E.; Thomas, Winston J.; **Wolff, Roger K.**

AB New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes contg. this mutation in their genomic DNA. PCR primers are described for HH diagnosis.

L4 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:41860 CAPLUS
DOCUMENT NUMBER: 126:55928
TITLE: Hereditary hemochromatosis gene point mutations as markers and PCR primers for disease diagnosis
INVENTOR(S): Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; Kimmel, Bruce E.; Thomas, Winston J.; **Wolff, Roger K.**
PATENT ASSIGNEE(S): Mercator Genetics, Inc., USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9635802	A1	19961114	WO 1996-US6352	19960506
W: AU, CA				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5753438	A	19980519	US 1995-436074	19950508
US 5705343	A	19980106	US 1996-599252	19960209
AU 9657282	A1	19961129	AU 1996-57282	19960506
ZA 9603639	A	19961119	ZA 1996-3639	19960508
PRIORITY APPLN. INFO.:			US 1995-436074 A	19950508
			US 1995-559302 A	19951115
			US 1996-599252 A	19960209
			WO 1996-US6352 W	19960506

AB New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes contg. this mutation in their genomic DNA. PCR primers are described for HH diagnosis.

IN Drayna, Dennis T.; Feder, John N.; Gnirke, Andreas; Kimmel, Bruce E.; Thomas, Winston J.; **Wolff, Roger K.**

AB New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes contg. this mutation in their genomic DNA. PCR primers are described for HH diagnosis.

L4 ANSWER 16 OF 17 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 96331279 MEDLINE
DOCUMENT NUMBER: 96331279 PubMed ID: 8696333
TITLE: A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis.
COMMENT: Comment in: Nat Genet. 1996 Aug;13(4):375-6
Comment in: Nat Genet. 1996 Nov;14(3):249-51
Comment in: Nat Genet. 1996 Nov;14(3):251-2
Comment in: Nat Genet. 1997 Mar;15(3):234
Comment in: Nat Genet. 1997 Mar;15(3):234-5
Comment in: Nat Genet. 1999 Nov;23(3):271
Comment in: Nat Genet. 1999 Nov;23(3):273-2
Comment in: Nat Genet. 1999 Nov;23(3):272
AUTHOR: Feder J N; Gnirke A; Thomas W; Tsuchihashi Z; **Ruddy D A**; Basava A; Dormishian F; Domingo R Jr; Ellis M C; Fullan A; Hinton L M; Jones N L; Kimmel B E; Kronmal G S; Lauer P; Lee V K; Loeb D B; Mapa F A; McClelland E; Meyer N C; Mintier G A; Moeller N; Moore T; Morikang E; **Wolff R K.**
CORPORATE SOURCE: Mercator Genetics, Inc., Menlo Park, California 94025, USA.
SOURCE: NATURE GENETICS, (1996 Aug) 13 (4) 399-408.
Journal code: BRO; 9216904. ISSN: 1061-4036.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-U60319
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19960912
Last Updated on STN: 20000407
Entered Medline: 19960905

AB Hereditary haemochromatosis (HH), which affects some 1 in 400 and has an estimated carrier frequency of 1 in 10 individuals of Northern European descent, results in multi-organ dysfunction caused by increased iron deposition, and is treatable if detected early. Using linkage-disequilibrium and full haplotype analysis, we have identified a 250-kilobase region more than 3 megabases telomeric of the major histocompatibility complex (MHC) that is identical-by-descent in 85% of patient chromosomes. Within this region, we have identified a gene related to the MHC class I family, termed HLA-H, containing two missense alterations. One of these is predicted to inactivate this class of proteins and was found homozygous in 83% of 178 patients. A role of this gene in haemochromatosis is supported by the frequency and nature of the major mutation and prior studies implicating MHC class I-like proteins in iron metabolism.

AU Feder J N; Gnirke A; Thomas W; Tsuchihashi Z; **Ruddy D A**; Basava A; Dormishian F; Domingo R Jr; Ellis M C; Fullan A; Hinton L M; Jones N L; Kimmel B E; Loeb D B; Mapa F A; McClelland E; Meyer N C; Mintier G A; Moeller N; Moore T; Morikang E; **Wolff R K.**

AB Hereditary haemochromatosis (HH), which affects some 1 in 400 and has an estimated carrier frequency of 1 in 10 individuals of Northern European.

L4 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1979:539883 CAPLUS
DOCUMENT NUMBER: 91:139883
TITLE: Electron structure and NMR parameters of substituted 5-phenyl-2,4-pentadienoic acids
AUTHOR(S): Radeglia, R.; **Wolff, R.**; Spanov, S.; Angelova, I.; Ivanov, Kh.
CORPORATE SOURCE: Zentralinst. Phys. Chem., Akad. Wiss., Berlin/Adlershof, Ger. Dem. Rep.
SOURCE: Org. Magn. Reson. (1978), 11(8), 390-4

```
                    CODEN: ORMRBD; ISSN: 0030-4921
DOCUMENT TYPE:      Journal
LANGUAGE:           German
AB   The 13C and 1H NMR chem. shifts and vicinal HH coupling consts.
     of 14 substituted 5-phenyl-2,4-pentadienoic acids are reported and
     discussed with ref. to their mol. structures.  The 13C chem. shifts
     alternate along the chain and were linearly correlated to .pi.-electron
     charge densities using the PPP method.  The effect of para substituents
     and solvents on the 13C chem. shifts is explained in terms of the mutual
     atom-atom polarizabilities.
AU   Radeglia, R.; Wolff, R.; Spasov, S.; Angelova, I.; Ivanov, Kh.
AB   The 13C and 1H NMR chem. shifts and vicinal HH coupling consts.
     of 14 substituted 5-phenyl-2,4-pentadienoic acids are reported and
     discussed with ref. to their mol. structures.  The 13C chem. shifts
     alternate along the chain and were linearly correlated to .pi.-electron
     charge densities using the PPP method.  The effect of para substituents
     and solvents on the 13C chem. shifts is explained in terms of the mutual
     atom-atom polarizabilities.


=>
=> s hh or hemochromotosis
L5          9272 HH OR HEMOCHROMOTOSIS

=> s l5 (P) 24dl
L6             0 L5 (P) 24D1

=> s l5 (P) 24dl
L7             0 L5 (P) 24DL

=> s l5 (P) (linkage or polymorphism?
UNMATCHED LEFT PARENTHESIS 'P) (LINKAGE'
The number of right parentheses in a query must be equal to the
number of left parentheses.

=> s l5 (P) (linkage or polymorphism?)
L8           304 L5 (P) (LINKAGE OR POLYMORPHISM?)

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PROCESSING COMPLETED FOR L8
L9           131 DUP REM L8 (173 DUPLICATES REMOVED)

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'19961523' NOT A VALID FIELD CODE
  3 FILES SEARCHED...
L10           25 L9 AND PD<19961523

=> dis l10 1-25 ibib abs kwic

L10  ANSWER 1 OF 25  CAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:       1995:283891  CAPLUS
DOCUMENT NUMBER:        122:56737
TITLE:                  Regiocontrolled Synthesis of Poly(3-alkylthiophenes)
                        Mediated by Rieke Zinc: Their Characterization and
                        Solid-State Properties
AUTHOR(S):              Chen, Tian-An; Wu, Xiaoming; Rieke, Reuben D.
CORPORATE SOURCE:       Department of Chemistry, University of
                        Nebraska-Lincoln, Lincoln, NE, 68588-0304, USA
SOURCE:                 J. Am. Chem. Soc. (1995), 117(1), 233-44
                        CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE:          Journal
LANGUAGE:               English
AB   A systematically regiocontrolled synthesis of poly(3-alkylthiophenes)
     (P3AT) mediated by Rieke zinc is reported.  Rieke zinc undergoes oxidative
     addn. to 2,5-dibromo-3-alkylthiophene or 2-bromo-5-iodo-3-alkylthiophene
     regioselectively to afford 2-bromo-5-(bromozincio)-3-alkylthiophene (2) or
     2-bromo-5-(iodozincio)-3-alkylthiophene (10).  The intermediate 2 or 10
     can be polymd. catalytically to a series of regiospecific
     poly(3-alkylthiophenes) using different catalysts.  The regioregularity of
     the polymer chain is solely controlled by the structure of the catalyst.
     An almost completely regioregular head-to-tail (HT) P3AT (4) is obtained
     by using Ni(DPPB)Cl2 [(1,2-bis(diphenylphosphino)ethane]nickel(II)
     chloride].  Use of Pd(DPPB)Cl2 leads to a redn. in the regioregularity
     (70:30 HT/HH), while using Ni(PPh)4 also leads to a much
     reduced regioregular P3AT (63:35 HT/HH).  A totally regiorandom
     (50:50 HT/HH) P3AT (5) is afforded by using Pd(PPh3)4.  The
     poly(3-butylthiophene) 4a is a 97% HT regioregular polymer.  Other
     poly(3-alkylthiophenes) (alkyl = hexyl (4b), octyl (4c), decyl (4d),
     dodecyl (4e), and tetradecyl (4f)) are regioregular P3ATs with the HT
     linkage larger than 98.5% based on NMR anal.  Electronic
     absorption, X-ray diffraction, and crossed polarizing micrograph studies
     show that the cast films of the regioregular P3ATs (4) are self-organized,
     cryst., flexible, and bronze-colored films with a metallic luster, while
     that of the regiorandom P3ATs (5) are amorphous and orange-colored films.
     The regioregular P3ATs exhibit a small bandgap (1.7 eV) which is 0.4 eV
     lower than that of regiorandom P3ATs (2.1 eV).  Regioregular HT P3ATs have
     considerably improved electrocond. and other phys. properties over
     regiorandom P3ATs.
SO   J. Am. Chem. Soc. (1995), 117(1), 233-44
     CODEN: JACSAT; ISSN: 0002-7863
AB   A systematically regiocontrolled synthesis of poly(3-alkylthiophenes)
     (P3AT) mediated by Rieke zinc is reported.  Rieke zinc undergoes oxidative
     addn. to 2,5-dibromo-3-alkylthiophene or 2-bromo-5-iodo-3-alkylthiophene
     regioselectively to afford 2-bromo-5-(bromozincio)-3-alkylthiophene (2) or
     2-bromo-5-(iodozincio)-3-alkylthiophene (10).  The intermediate 2 or 10
     can be polymd. catalytically to a series of regiospecific
     poly(3-alkylthiophenes) using different catalysts.  The regioregularity of
     the polymer chain is solely controlled by the structure of the catalyst.
     An almost completely regioregular head-to-tail (HT) P3AT (4) is obtained
     by using Ni(DPPB)Cl2 [(1,2-bis(diphenylphosphino)ethane]nickel(II)
     chloride].  Use of Pd(DPPB)Cl2 leads to a redn. in the regioregularity
     (70:30 HT/HH), while using Ni(PPh)4 also leads to a much
     reduced regioregular P3AT (63:35 HT/HH).  A totally regiorandom
     (50:50 HT/HH) P3AT (5) is afforded by using Pd(PPh3)4.  The
     poly(3-butylthiophene) 4a is a 97% HT regioregular polymer.  Other
     poly(3-alkylthiophenes) (alkyl = hexyl (4b), octyl (4c), decyl (4d),
     dodecyl (4e), and tetradecyl (4f)) are regioregular P3ATs with the HT
     linkage larger than 98.5% based on NMR anal.  Electronic
     absorption, X-ray diffraction, and crossed polarizing micrograph studies
     show that the cast films of the regioregular P3ATs (4) are self-organized,
     cryst., flexible, and bronze-colored films with a metallic luster, while
     that of the regiorandom P3ATs (5) are amorphous and orange-colored films.
     The regioregular P3ATs exhibit a small bandgap (1.7 eV) which is 0.4 eV
```

lower than that of regiorandom P3ATs (2.1 eV). Regioregular HT P3ATs have considerably improved electrocond. and other phys. properties over regiorandom P3ATs.

L10 ANSWER 2 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:531088 CAPLUS
DOCUMENT NUMBER: 121:131088
TITLE: Iron metabolism and hereditary hemochromatosis: an update
AUTHOR(S): Camaschella, C.; Roetto, A.
CORPORATE SOURCE: Osp. San Luigi Gonzaga, Univ. Torino, Torin, Italy
SOURCE: Bull. Mol. Biol. Med. (1994), 19(1), 21-32
CODEN: BMBMDS; ISSN: 0391-481X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 32 refs. Iron is essential for life but highly toxic to the cell when present in excess. This is well exemplified by Hereditary Hemochromatosis (HH), an autosomic recessive disorder which causes iron overload during adult life. The biochem. abnormality of the disease is still unknown, but likely due to a deregulation of intestinal iron absorption. The tight linkage of HH with HLA-A locates the gene on the short arm of chromosome 6. The study of mol. markers close to HLA class I in HH families has narrowed the candidate region. All this DNA area is available cloned in YAC vectors and this will facilitate the discovery of the gene. The identification of the gene and of its mol. defects will be a major advance towards the screening of populations at risk and the understanding of physiol. mechanisms of iron metab.
SO Bull. Mol. Biol. Med. (1994), 19(1), 21-32
CODEN: BMBMDS; ISSN: 0391-481X
AB A review, with 32 refs. Iron is essential for life but highly toxic to the cell when present in excess. This is well exemplified by Hereditary Hemochromatosis (HH), an autosomic recessive disorder which causes iron overload during adult life. The biochem. abnormality of the disease is still unknown, but likely due to a deregulation of intestinal iron absorption. The tight linkage of HH with HLA-A locates the gene on the short arm of chromosome 6. The study of mol. markers close to HLA class I in HH families has narrowed the candidate region. All this DNA area is available cloned in YAC vectors and this will facilitate the discovery of the gene. The identification of the gene and of its mol. defects will be a major advance towards the screening of populations at risk and the understanding of physiol. mechanisms of iron metab.

L10 ANSWER 3 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:161390 CAPLUS
DOCUMENT NUMBER: 120:161390
TITLE: Polymorphic Hh genes in the HLA-B(C) region control natural killer cell frequency and activity
AUTHOR(S): Dubey, Devendra P.; Alpet, Chester A.; Mirza, Nadeem M.; Awdeh, Zuheir; Yunis, Edmond J.
CORPORATE SOURCE: Div. Immunogen., Dana-Farber Cancer Inst., Boston, MA, 02115, USA
SOURCE: J. Exp. Med. (1994), 179(4), 1193-203
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It was demonstrated earlier that individuals homozygous for conserved major histocompatibility complex (MHC)-extended haplotypes have low natural killer (NK) activity as measured by cytolysis of the K562 tumor cell line. In the present study, the authors investigated the segregation and MHC linkage of NK activity in families in which MHC haplotypes of human histocompatibility leukocyte antigens (HLA)-A, -C, and -B, complotype, and DR specificities are known. In two informative families, low activity was inherited as a recessive trait linked to the MHC. By using individuals homozygous for specific fragments of extended haplotypes or for HLA-B alleles, the authors found that the HLA-C and -B and not the complotype or HLA-DR region contains genes controlling NK activity. The majority of the unrelated individuals with low NK activity were homozygous or doubly heterozygous for HLA-B7 (Cw7), B8 (Cw7), B44 (Cw5), B18, or B57 (Cw6). Thus, these alleles form one complementation group designated NKb1. Another less frequent group, NKb2, was also identified, and consisted of individuals homozygous for B35 (Cw4). NK activity was correlated with the no. of circulating NK (CD16+CD56+) cells. Individuals homozygous for the NKb complementation groups have fewer circulating NK cells than individuals heterozygous for these alleles and alleles of other complementation groups, possibly explaining the low activity of cells in these subjects. Thus, during the maturation of NK cells there is NK cellular deletion in donors homozygous for NKb genes resulting in low NK cell nos. and activity.
SO J. Exp. Med. (1994), 179(4), 1193-203
CODEN: JEMEAV; ISSN: 0022-1007
IT Gene, animal
RL: BIOL (Biological study)
(Hh, within HLA-B(C) region, **polymorphism** of, human natural killer frequency and activity in relation to)
IT Genetic **polymorphism**
(of Hh genes within HLA-B(C) region, human natural killer frequency and activity in relation to)

L10 ANSWER 4 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:137269 CAPLUS
DOCUMENT NUMBER: 120:137269
TITLE: Intercalated antimicrobial compound-containing coatings
INVENTOR(S): Yoshioka, Katsuaki
PATENT ASSIGNEE(S): Nippon Paint Co Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAP
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05140482	A2	19930608	JP 1991-326388	19911114 <--

AB The title coatings contain binders, and intercalated compds. prepd. from clays, amine or quaternary ammonium salt-type cationic surfactants contg. .gtoreq.2 C.gtoreq.10 alkyl groups and .gtoreq.1 ester ether or amido **linkages**, and antimicrobial materials. A compn. contg. Luviskol K 30, SMR 30 **HH** (polyvinyl pyrrolidone), and an intercalated compd. [from Kunipia F, R1OCH2CHOHCH2NR2R3R4 X- (R1 = C10 alkyl; R2 = C16

alkyl, R3, R4 = Me; X = Cl), and Japanese Cypress leaf oil) was spread on a chromated Al plate and showed good antimicrobial ability (JIS Z 2911) at 27.degree. over 1 wk.

PI JP 05140482 A2 19930608 Heisei

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05140482	A2	19930608	JP 1991-326388	19911114 <--

AB The title coatings contain binders, and intercalated compds. prepd. from clays, amine or quaternary ammonium salt-type cationic surfactants contg. .gtoreq.2 C.gtoreq.10 alkyl groups and .gtoreq.1 ester ether or amido **linkages**, and antimicrobial materials. A compn. contg. Luviskol K 30, SMW 30 MW (polyvinyl pyrrolidone), and an intercalated compd. [from Kunipia F, R1OCH2CHOHCH2NR2R3R4 X- (R1 = C10 alkyl; R2 = C16 alkyl, R3, R4 = Me; X = Cl), and Japanese Cypress leaf oil] was spread on a chromated Al plate and showed good antimicrobial ability (JIS Z 2911) at 27.degree. over 1 wk.

L10 ANSWER 5 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:8021 CAPLUS
DOCUMENT NUMBER: 112:8021
TITLE: Thermal degradation of poly(methyl methacrylate). 3. Polymer with head-to-head linkages
AUTHOR(S): Manring, Lewis E.; Sogah, Dotsevi Y.; Cohen, Gordon M.
CORPORATE SOURCE: Cent. Res. Dev. Dep., E. I. du Pont de Nemours and Co., Inc., Wilmington, DE, 19898, USA
SOURCE: Macromolecules (1989), 22(12), 4652-4
CODEN: MAMOBX; ISSN: 0024-9297
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The thermal degrdn. of PMMA in which each chain contains one head-to-head bond (PMMA-HH) is compared to the thermal degrdn. of satd. PMMA which contains no weak links (PMMA-H). The presence of head-to-head **linkages** can reduce PMMA-HH stability relative to PMMA-H. However, a large cage effect leads predominantly to radical recombination which reduces the amt. of polymer degrdn. initiated by head-to-head bond cleavage. The obsd. extent of the polymer destabilization is inconsistent with proposed mechanisms for PMMA degrdn.

SO Macromolecules (1989), 22(12), 4652-4
CODEN: MAMOBX; ISSN: 0024-9297

AB The thermal degrdn. of PMMA in which each chain contains one head-to-head bond (PMMA-HH) is compared to the thermal degrdn. of satd. PMMA which contains no weak links (PMMA-H). The presence of head-to-head **linkages** can reduce PMMA-HH stability relative to PMMA-H. However, a large cage effect leads predominantly to radical recombination which reduces the amt. of polymer degrdn. initiated by head-to-head bond cleavage. The obsd. extent of the polymer destabilization is inconsistent with proposed mechanisms for PMMA degrdn.

L10 ANSWER 6 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:110281 CAPLUS
DOCUMENT NUMBER: 104:110281
TITLE: Chain length dependency of head-to-head addition in the radical polymerization of allyl monomers
AUTHOR(S): Matsumoto, Akira; Kikuta, Manabu; Oiwa, Masayoshi
CORPORATE SOURCE: Fac. Eng., Kansai Univ., Suita, 564, Japan
SOURCE: J. Polym. Sci., Polym. Lett. Ed. (1986), 24(1), 7-11
CODEN: JPYBAN; ISSN: 0360-6384
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The factors influencing the addn. modes in the radical polymn. of alkyl esters were studied. The percentage of head-to-head (HH) **linkage** decreased with increasing d.p. The chain length dependency of HH addn. was ascribed to the steric effect of side chains on the intermol. HH addn. Thus, the steric crowding at a terminal radical site by side chains would increase with the chain length and the bulkiness and polarity of the side chains. The chain length dependency of HH **linkage** became remarkable in the order allyl benzoate .simeq. allyl acetate < allyl glycolate < allyl chloroformate < allyl dichloroacetate < allyl trichloroacetate.

SO J. Polym. Sci., Polym. Lett. Ed. (1986), 24(1), 7-11
CODEN: JPYBAN; ISSN: 0360-6384

AB The factors influencing the addn. modes in the radical polymn. of alkyl esters were studied. The percentage of head-to-head (HH) **linkage** decreased with increasing d.p. The chain length dependency of HH addn. was ascribed to the steric effect of side chains on the intermol. HH addn. Thus, the steric crowding at a terminal radical site by side chains would increase with the chain length and the bulkiness and polarity of the side chains. The chain length dependency of HH **linkage** became remarkable in the order allyl benzoate .simeq. allyl acetate < allyl glycolate < allyl chloroformate < allyl dichloroacetate < allyl trichloroacetate.

L10 ANSWER 7 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1984:121658 CAPLUS
DOCUMENT NUMBER: 100:121658
TITLE: Studies of the polymerization of diallyl compounds. XL. Correlation between addition modes and evolution of carbon dioxide in the polymerization of diallyl oxalate
AUTHOR(S): Yamawaki, Masataka; Kikuta, Manabu; Matsumoto, Akira; Oiwa, Masayoshi
CORPORATE SOURCE: Fac. Eng., Kansai Univ., Suita, 564, Japan
SOURCE: J. Macromol. Sci., Chem. (1984), A21(2), 207-14
CODEN: JMCHBD; ISSN: 0022-233X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The occurrence of head-to-head (HH) addn. in the radical polymn. of diallyl oxalate (I) [615-99-6] was examd. under various polymn. conditions. The content of HH **linkage** in the polymer was reduced in comparison with that previously reported for allyl acetate and diallyl succinate; this could be ascribed to the high polarity of I inducing a polar effect on the intermol. propagation of the growing polymer radical, resulting in reduced HH addn. The correlation between the addn. modes and the evolution of CO2 characteristic of I polymn. at elevated temps. was discussed mechanistically in detail, with special focus on the solvent effect and the reduced diemutation of the cyclized radical compared to the uncyclized one.

SO J. Macromol. Sci., Chem. (1984), A21(2), 207-14
CODEN: JMCHBD; ISSN: 0022-233X

AB The occurrence of head-to-head (HH) addn. in the radical polymn. of diallyl oxalate (I) [615-99-6] was examd. under various polymn.

conditions. The content of HH linkage in the polymer was reduced in comparison with that previously reported for allyl acetate and diallyl succinate; this could be ascribed to the high polarity of I inducing a polar effect on the intermol. propagation of the growing polymer radical, resulting in reduced HH addn. The correlation between the addn. modes and the evolution of CO2 characteristic of I polymn. at elevated temps. was discussed mechanistically in detail, with special focus on the solvent effect and the reduced dismutation of the cyclized radical compared to the uncyclized one.

L10 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1975:595518 CAPLUS
DOCUMENT NUMBER: 83:195518
TITLE: Lignin. XVII. Preparation and characterization of acetyl lignin sulfonate methyl esters
AUTHOR(S): Glasser, Wolfgang G.; Gratzl, Josef S.; Collins, Juanita J.; Forss, Kaj; McCarthy, Joseph L.
CORPORATE SOURCE: Dep. Chem. Eng., Univ. Washington, Seattle, Wash., USA
SOURCE: Macromolecules (1975), 8(5), 565-73
CODEN: MAMOBX
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Western Hemlock wood chips were deligntified with aq. SO2 soln. and CaO and the resultant lignin sulfonates were fractionated by Sephadex G-25, acetylated with Ac2O and methylated with MeI to give .apprx.80% Me lignosulfonate acetate (I) which was characterized by NMR and chem. anal. I was also prepd. from milled wood lignin [8068-00-6]. Satisfactory acetylation was accomplished after inauguration of a preliminary step consisting of freeze drying and then reswelling the ligninsulfonate. The Me esters were prepd. through the Ag salt. The functional groups in I were detd. from the formulation: C9H.alpha.Ob[(Hc[OH)d(OMe)e(-O-)f-(-)g]arom. [(Hh[OH)i(-)j(-)k(SO3H)l]aliph. where (-O-)f = arom. ether linkages, (-)g = arom. C linkages, (-)j = aliph. ether linkages, (-)k = aliph. C linkages, (SO3H)l + total SO3H grouping. Aliph. Ac groups = 0.9/C9 unit. Total MeO = 1.10 Me/C9. Total sulfonate groups = 0.35/C0 unit. The no. of sulfonate Me esters/C9 unit = 0.20. A cryst. substance, m. 202-3.degree. and a glassy amber material which softened at 80-90.degree. and melted with decompn. at 150-60.degree. were isolated by column chromatog. on Sephadex gel LH20.
SO Macromolecules (1975), 8(5), 565-73
CODEN: MAMOBX
AB Western Hemlock wood chips were deligntified with aq. SO2 soln. and CaO and the resultant lignin sulfonates were fractionated by Sephadex G-25, acetylated with Ac2O and methylated with MeI to give .apprx.80% Me lignosulfonate acetate (I) which was characterized by NMR and chem. anal. I was also prepd. from milled wood lignin [8068-00-6]. Satisfactory acetylation was accomplished after inauguration of a preliminary step consisting of freeze drying and then reswelling the ligninsulfonate. The Me esters were prepd. through the Ag salt. The functional groups in I were detd. from the formulation: C9H.alpha.Ob[(Hc[OH)d(OMe)e(-O-)f-(-)g]arom. [(Hh[OH)i(-)j(-)k(SO3H)l]aliph. where (-O-)f = arom. ether linkages, (-)g = arom. C linkages, (-)j = aliph. ether linkages, (-)k = aliph. C linkages, (SO3H)l + total SO3H grouping. Aliph. Ac groups = 0.9/C9 unit. Total MeO = 1.10 Me/C9. Total sulfonate groups = 0.35/C0 unit. The no. of sulfonate Me esters/C9 unit = 0.20. A cryst. substance, m. 202-3.degree. and a glassy amber material which softened at 80-90.degree. and melted with decompn. at 150-60.degree. were isolated by column chromatog. on Sephadex gel LH20.

L10 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1970:485922 CAPLUS
DOCUMENT NUMBER: 73:85922
TITLE: Synthesis and secretion of .gamma.-globulin by lymph node cells. VIII. Order of synthesis of the interchain disulfide linkages of immunoglobulins
AUTHOR(S): Sutherland, Earl W., III; Zimmerman, Daniel H.; Kern, Milton
CORPORATE SOURCE: Nat. Inst. of Arthritis and Metabol. Dis., Nat. Inst. of Health, Bethesda, Md., USA
SOURCE: Proc. Nat. Acad. Sci. U. S. (1970), 66(3), 987-94
CODEN: PNASA6
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Murine myeloma cells (ADJ-PC-5), incubated in vitro with leucine-3H, secrete immunoglobulin G-3H as a single mol. species as judged by the migration characteristics of the labeled product on Na dodecyl sulfate-acrylamide gel electrophoresis. However, the fact that some of the interchain SS linkages of intracellular immunoglobulins had not been acquired permitted the identification of the following intracellular species: LHHL (identical to immunoglobulin G), HHL, HH, and L (H and L refer to heavy and light polypeptide chains, resp.). Although HH and HHL were readily observed, radioactivity was not detected in the region of the gel where HL would be expected. The time course for the appearance of the intermediates indicates that in these cells the 1st interchain SS bond to be formed occurs between heavy chains. In contrast, the interchain SS bonds of immunoglobulins derived from rabbit lymph node cells were acquired in a different order. The principal intracellular species observed were LHHL and HL, whereas HHL and HH were not detectable. These findings indicate that in this species the 1st interchain SS bond to be formed is that between the heavy and light chains of immunoglobulin G.
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L10 ANSWER 10 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1939:58921 CAPLUS
DOCUMENT NUMBER: 33:58921
ORIGINAL REFERENCE NO.: 33:8459e-f
TITLE: Interrelation of dissociation energy and internuclear distance for some simple diatoms in ground states
AUTHOR(S): Clark, C. H. Douglas
SOURCE: Nature (1939), 144, 285-6
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C. A. 33, 5245.8,5245.9. Work on the relation between dissocn. energy and internuclear distance of C-C linkages is extended to diatoms of the HH, KH and KK periods in ground states. This leads to new functions involving bond const. and internuclear distance, having characteristic values in given periods for diatoms of similar electronic configuration. Extension to excited states appears possible.
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L10 ANSWER 11 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1929:2877 CAPLUS
DOCUMENT NUMBER: 23:2877
ORIGINAL REFERENCE NO.: 23:393I,393a-e
TITLE: Alkaloids of Sinomonium and Coccuius. XXI. Constitution of trilobine and homotrilobine
AUTHOR(S): Kondo, H.; Tomita, M.
CORPORATE SOURCE: Tokyo Imp. Univ.
SOURCE: J. Pharm. Soc. Japan (1928), 48, 659-73
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
AB cf. C. A. 19, 1708; 21, 2699. Previously (C. A. 21, 2699) it was reported that trilobine (I) and 2 other bases were isolated from Cacculus sarmentosus. One of the latter has now been proved to be homotrilobine (II), C20H21NO3 (m. 215.degree., [.alpha.]D8 314.8.degree.). It contains one MeO group. In contrast to I, the HBr salt of II is more sol. in H2O and Me2CO. II and MeI gave the methiodide (III), m. 262-5.degree.. Heating of III with 20% KOH-MeOH gave .alpha.-homotrilobinemethylmethin (IV), C31H23NO3, (m. 115-7.degree., [.alpha.]D12 and a small quantity of .beta.-homotrilobinemethylmethine, m. 222.degree.. IV and MeI gave .alpha.-homotrilobinemethylmethine-MeI (V), m. 264.degree., which on boiling with KOHMeOH gave beside NMe3, a non-N compd. C18H13O2(OMe), m. 185.degree.. II and Ac2O gave, as a result of the rupture of the N-ring, a non-basic substance m. 285-7.degree.. Heating of II with HBr in glacial AcOH is a closed tube resulted in the opening of the O-ring and gave a substance m. 270.degree.. The above reactions show that contrary to the previous statement, II contains one N-Me group instead of a NMe2 group and its structure can be expressed by C18H16O(OMe)(NMe)(=O). It was previously suggested that 2 O atoms in I form either an ether linkage or a special (-CO-) group. The action of Ac 2O or ClCO2Et on I resulted only in the decompn. of the N-ring, but without any change in the groups contg. O atoms. The action of HBr in glacial AcOH on I, however, resulted in the rupture of the O-ring and gave a compd. contg. a newly formed OH group and a double bond originated as a result of the sepn. of another OH group in the form of H2O. The compd. is named desmethyltrilobinol (VI), C18H17NO3, m. 290.degree., [.alpha.] D18 229.3.degree.. HBr salt decomps. 315 .degree.. With EtOH, VI forms an addn. compd. (VII) which loses EtOH on heating above 130.degree.. It has no MeO group. The no. of OH groups as detd. by Zerevitiuov's method on VII was 3, while VI contained only 2. VI and Ac2O gave the di-Ac deriv., m. 210.degree., [.alpha.]D29.5 302.1.degree.. KOH fusion of VI gave 3,4-(HO)2C6H3CO2H and 1,2-(HO)2C6H4. Oxidation of I with dil. KMnO4 gave a glycol, C19H31NO3, m. 265.degree.. Further oxidation gave an intermediate dicarboxylic acid, decompn. 210-20.degree., and finally des.-N-trilobinedicarboxylic acid (VIII), C15H16O7, m. 288.degree.. Action of HBr in glacial AcOH on VIII gave desmethyl-des-N-trilobinoldicarboxylic acid (IX), C17H14O7, m. 278-9.degree. (decompn.). Heating of VIII with HI gave desmethyl-des-N-trilobinedicarboxylic acid, m. 267.degree., which with HBr in glacial AcOH gave also IX. The above reactions can be explained in a similar way as in the production of VI by the action of HBr on I. From the oxidation reactions and also from the fact that VIII gave a phthalein reaction, it is concluded that the position of double bond in I is like that of naphtha. quinoline or acenaphthylene.
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AB cf. C. A. 19, 1708; 21, 2699. Previously (C. A. 21, 2699) it was reported that trilobine (I) and 2 other bases were isolated from Cacculus sarmentosus. One of the latter has now been proved to be homotrilobine (II), C20H21NO3 (m. 215.degree., [.alpha.]D8 314.8.degree.). It contains one MeO group. In contrast to I, the HBr salt of II is more sol, in H2O and Me2CO. II and MeI gave the methiodide (III), m. 262-5.degree.. Heating of III with 20% KOH-MeOH gave .alpha.-homotrilobinemethylmethin (IV), C31H23NO3, (m. 115-7.degree., [.alpha.]D12 and a small quantity of .beta.-homotrilobinemethylmethine, m. 222.degree.. IV and MeI gave .alpha.-homotrilobinemethylmethine-MeI (V), m. 264.degree., which on boiling with KOHMeOH gave beside NMe3, a non-N compd. C18H13O2(OMe), m. 185.degree.. II and Ac2O gave, as a result of the rupture of the N-ring, a non-basic substance m. 285-7.degree.. Heating of II with HBr in glacial AcOH is a closed tube resulted in the opening of the O-ring and gave a substance m. 270.degree.. The above reactions show that contrary to the previous statement, II contains one N-Me group instead of a NMe2 group and its structure can be expressed by C18H16O(OMe)(NMe)(=O). It was previously suggested that 2 O atoms in I form either an ether linkage or a special (-CO-) group. The action of Ac 2O or ClCO2Et on I resulted only in the decompn. of the N-ring, but without any change in the groups contg. O atoms. The action of HBr in glacial AcOH on I, however, resulted in the rupture of the O-ring and gave a compd. contg. a newly formed OH group and a double bond originated as a result of the sepn. of another OH group in the form of H2O. The compd. is named desmethyltrilobinol (VI), C18H17NO3, m. 290.degree., [.alpha.] D18 229.3.degree.. HBr salt decomps. 315 .degree.. With EtOH, VI forms an addn. compd. (VII) which loses EtOH on heating above 130.degree.. It has no MeO group. The no. of OH groups as detd. by Zerevitiuov's method on VII was 3, while VI contained only 2. VI and Ac2O gave the di-Ac deriv., m. 210.degree., [.alpha.]D29.5 302.1.degree.. KOH fusion of VI gave 3,4-(HO)2C6H3CO2H and 1,2-(HO)2C6H4. Oxidation of I with dil. KMnO4 gave a glycol, C19H31NO3, m. 265.degree.. Further oxidation gave an intermediate dicarboxylic acid, decompn. 210-20.degree., and finally des.-N-trilobinedicarboxylic acid (VIII), C15H16O7, m. 288.degree..

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L10 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1922:14323 CAPLUS
DOCUMENT NUMBER: 16:14323
ORIGINAL REFERENCE NO.: 16:2475g-i,2476a-i,2477a-i,2478a-i,2479a-c
TITLE: The acid aldehydes of the succinic series
AUTHOR(S): Carriere, E.
SOURCE: Ann. chim. (1921), 17, 38-132
DOCUMENT TYPE: Journal
LANGUAGE: Unavailable
GI For diagram(s), see printed CA issue.

AB The object of the work was to study a general method for prepg. aldehyde acids, certain of which have been prepd. in small yield by Harries and Tank (C. A. 2, 2375) who decompd. ozonides with H2O (also C. A. 3, 183, and Ann. 343, 359(1905)). These compds. have also been found among the oxidation products of unsatd. acids (Ann. 143, 34(1867); 140, 66(1866); Ber. 34, 1500(1901); Bull. soc. chim. [3] 31, 161(1904); Ber. 33, 2763(1900)). Perkin and Sprankling prepd. HO2C(CH2)2CHO (A) by condensing CNNa(CO2Et)2 with MeCBr(OEt)2 (J. Chem. Soc. 75, 16(1899)). Frankenstein (Diss. Koenigsberg 1899), and von Ungern Sternberg (Diss. Koenigsberg 1906) prepd. A by decompg. aconic acid (B) with H2O. Homologs of A cannot be prepd. by this method because homologs of B are not known. Harries and Alefeld formed A in 10% yield by decompg. the ozonide of allylacetic acid with H2O. OHCCH(CO2Et)CH2CO2Et (F) was prepd. by Willicenus, Boklen and Reuthe (C. A. 3, 790) by condensing HCO2Et (C) with EtO2CCH2CHCO2Et (D) but C. found that NaOEt gave good results. To 27.6 g. Na as NaOEt was added in small amts., 174 g. D with 89 g. C and after the mixt. stood in the cold for several days. OHCCH(CO2Et)CHNaCO2Et (E) sepd. It was then treated with H2SO4, extd. with Et2O and the calcd. amt. of F, b15 128-148.degree., was obtained. The range is wide because of the presence of the enolic and aldehyde forms. The Meyer technic was used for the study of the equil. (C. A. 8, 1774). The enolic form in F after standing several hrs. was 50% and in a 4.643% soln. in alc. fell to 12% at the end of 4 days. On distn. the first portion contained 30% of enolic F and the last portion 60%. All fractions at the end of several hrs. contained 50% enolic F and the sepn. could not be effected by distn. Ethyl formylsuccinate semicarbazone (CC), white crystals, m. 126.degree., and the p-nitrophenylhydrazone, yellow crystals, m. 100.degree.. Et benzoylformylsuccinate was prepd. by condensing F with BzCl, b14 208-12.degree. (not in accord with the value given by W., R., and B.), needles m. 58-9.degree.. The action of PhNH2 and certain of its derivs. on F was studied. From the product resulting when F interacted with PhNH2 ethyl anilinoitaconate, yellow crystals, m. 102.degree., was obtained. Ethyl p-toluidinoitaconate (G) was prepd. in a similar manner. G sapond. with alc. KOH gave ethyl 1-p-cresyl-3-carboxylate-5-pyrrolinone (J), MeC5H4N.CH:C(CO2Et).CH2.CO, yellow crystals, m. 123-4.degree.. Ethyl benzylaminoitaconate (H) was prepd. by treating F with PhCH2NH2, white crystals, m. 54.degree., and H when treated with alc. KOH followed by HCl gave ethyl 1-benzylamino-3-carboxylate-5-pyrrolinone, yellow crystals, m. 95.degree.. J when sapond. by NaOH gave a small amt. of p-H2NC6H4Me and when the mixt. was treated with H2SO4, HCO2H and (CH2CO2H)2 were formed. NH2OH.HCl and K2CO3 mixed with F gave ethyl formylsuccinate oxime (K), viscous liquid which on distn. gave ethyl .beta.-cyanopropionate (L), b18 114-5.degree.. L sapond. with KOH gave (CH2CO2H)2. Succinic acid aldehyde oxime, HON:CHCH2CH2CO2H, white crystals, m. 155.degree.. K when heated is dehydrated and the H2O resulting from this action sapons. the ester group .beta. to the CN group, the CO2H group losing CO2 with formation of L. In prepg. (RO2C)2CHCHBrCO2Et (M) BrCHBrCO2Et was first prepd. by the method of Hell, Volhard and Zelinsky and this was then condensed with CNNa(CO2Et)2. The resulting tri-ester was sapond. by heating it 12 hrs. with HCl. The H2O and HCl were eliminated in vacuo and the residue was heated in an oil bath at 150-60.degree. to transform the carboxyethylsuccinic acid into EtCH(CO2H)CH2CO2H (N), of which a 78% yield was obtained (Ann. 192, 148(1878)). N was esterified to M, using alc. N, when heated with AcCl, gave EtCH.CO.O.CO.CH2 (O), b20 140.degree. (Ann. 291, 121(1896)), which with PhNH2 in CsH6 gave ethyl succinic acid anilide (P), crystals from alc., m. 118.degree.. P heated at 180.degree. during 1.5 hrs. gave ethylsuccinic anil, crystals m. 74.degree.. O heated 6 hrs. with PCl5 gave ethylsuccinyl chloride, EtCH(COCl)CH2COCl, b14 94-5.degree., and when this compd. was treated with PhNH2 in Et2O ethylsuccinic dianilide, crystals, m. 205.degree., was formed. Ethyl formylethylsuccinate (Q) was prepd. by treating HCO2Et and M with NaOEt in Et2O in the cold for 3 days. H2SO4 was then added and Q sepd. and after treatment with K2CO3 and distn. was obtained (68% yield) as an oil, b15 145-70.degree.. The enolic form HOCH:C(CO2Et)CHEtCO2Et and the aldehydic form OHCCH(CO2Et)CHEtCO2Et exist and the equil. between these 2 forms as detd. by the Meyer technic was found to be attained slowly. An initial enol content of 37% fell to 17% in 3 weeks. The deriv. of the aldehydic form were the semicarbazone, white crystals from alc., m. 113.degree. the p-nitrophenylhydrazone, m. 113.degree., from AcH. The deriv. from the enolic form were the phenylurethan and the benzoate (the product reported as the phenylurethan was made by condensing Q with BzCl in C5H5N, b14 220.degree. (C14H22O6). Abstr.). Ethyl 1-phenyl-4-carboxylate-5-ethyl-6-pyridisinone, EtCH.CO.NPh.N:CH.CHCO2Et (R), b15 225-40.degree., crystals from alc., was prepd. by heating Q with PhNHNH2; it was sapond. with NaOH to the free acid, crystals m. 179.degree.. Q with PhNH2 gave a thick liquid, ethyl anilinoethylitaconate, EtO2CCHELCH(:CNHNPh)CO2Et, which when sapond. with alc. KOH followed by HCl treatment gave 1-phenyl-4-ethyl-3-carboxyl-5-pyrrolinone (S), EtCH.CO.NPh. CH:CCO2H, yellow crystals from alc., m. 190.degree. (decompn.). Q interacted with p-MeC6H4NH2 and the resulting ethyl p-toluidinoethylitaconate was sapond. with KOH, yielding 1-p-cresyl-4-ethyl-3-carboxyl-5-pyrrolinone (T), yellow crystals from alc., m. 203.degree.. S gave the corresponding ester when treated with alc. and HCl, crystals from alc., m. 99.degree., and T gave the corresponding ester, m. 104.degree.. The equation for the transformation of F into A is: F + 2H2O = CO2 + alc. +A. A curve showing the rate of hydrolysis of F by (CO2H)2 is given, a max. being reached in 1 hr. The reaction was followed by the amt. of CO2 evolved. The (CO2H)2 was eliminated from the mixt. resulting from the hydrolysis by titration with Ca(OAc)2. The CaC2O4 was filtered and the ether ext. distd. in vacuo gave A, b15 142-3.degree. (45% yield) (Harries and Alefeld gave b14 134-6.degree.; C. A. 3, 895). (CH2CO2H)2 was also formed. According to the method of von Ungern Sternburg a 50% yield of A is obtained and the transformation of itaconic acid into B is only to the extent of 60%,

whereas the transformation of (CH2CO2Et)2 into F is quant . A gives with the Schiff reagent a violet color, MH3AgNO3 is reduced at once in the cold as well as is Fehling soln. The semicarbazone m. 194-5.degree. (decompn.) (H. and A. gave 177-8.degree.). The p-nitrophenylphenylhydrazone m. 180-1.degree. (and not at 175.degree.; C. A. 3, 2154). The oxime, white crystals, m. 102-8.degree.. Naphthocinchoninylpropionic acid was prepd. by dissolving C10H7NH2 in alc. with AcCO2H and A and heating the mixt. 2 hrs., yellow crystals from HCO2H and H2O mixt. A was reduced with Hg-Na to O.CO.CH2.CH2.CH2.O and this lactone with NH4NH2.H2O gave butyrolactone hydrazone, H2NNHC(OH).CH2.CH2.CH2.O, leaves from AcOEt, m. 93.degree.. The calcium salt of A was prepd. and the phenylhydrazone. A with H2SO4 polymerizes to the trimer HO2C(CH2)2CHCH(CH2)2CO2H, m. 167, slightly sol. in Et2O, CH(CH2)2CO2H AcOEt, and in Na2CO3 but the aldehydic properties are masked-there is no coloration with the Schiff reagent, no semicarbazone, p-nitrophenylhydrazone, nor oxime could be formed, and the product did not reduce NH2-AgN3. The bonds forming the cycle are attached to the O atoms. References to this compd. are given. The dimer m. 147.degree. (C. A. 6, 1749). The trimer when distd. gave A and hydroxybutyrolactone oxide, (O.CO.CH2.CH2.CH-)2O. A can exist as hydroxybutyrolactone. Elimination of H2O from this compd. would lead to the oxide. The oxide when treated with semicarbazide gave the semicarbazone of A and when treated with alc.-HCl, OHCCH(CHCO2Et was formed. With NaOH the Na salt of A is formed and when the latter is acidified aldolization results in the formation of butyrolactone aldehyde succinic acid, O.CO.CH2CHCH(CHO)CH2CO2H, which yields a semicarbazone, white powder, slightly sol. in alc., m. 225.degree.. SOCl2 or PCl5 when acting on A as the trimer gave chlorobutyrolactone, b15 101.degree., which when distd. loses HCl and when treated with aba. alc. gave ethyl acetalsuccinate, EtO2CCH2CHCH2CH(OEt)2. C. discusses the relation between B, itaconic acid, F and A and he reproduces the work of Swarts (Bull. acad. roy. Belg. [2] 13, 1873). CH2BrCHr(CO2H).CH2CO2H (AA) was heated at 180.degree. and bromoitaconic acid, m. 190-5.degree., was prepd. This on treatment with H2O gave B, m. 170.degree.. AA when heated with H2O gave B. C. concluded that considering the monohalogenated acids prepd. by Wislicenus, Boklen and Reuthe and by Swarts, the true mono-Cl deriv. was obtained by the former experimenters among the products of the action of PCl5 on F. C. believes that Swarts' product is CH2.CH2.O.CH.CBrCO2H and that Frankenstein's hydroxyitaconic acid (Diss. p. 22-31) is formylsuccinic acid (DD) in the enolic form, HOCH:C(CO2H)CH2CO2H. CC treated in aba. alc. with KOH gave after elimination of alc. and treatment with HCl, N - 3 - carbamyl - 4 - acetyl - 5 - pyrazolone, HO2CCH2CH.CH:N.NCONH2).CO (EE), crystals, m. 185.degree., which result from the loss of a mole of H2O from the semicarbazone of DD. To throw light on the course of the reaction taking place when CC is hydrolyzed, C. sapond. MeC:N.NH.CO.NH.CH2CO2Et and prepd. by this means N-1-carbamyl-3-methyl-5-pyrazolone, m. 170.degree., which with FeCl3 gave a violet coloration (Compt. rend. 132, 975(1901)). A was esterified in alc. with HCl during 40 hrs., yielding ethyl aldehydosuccinate (FF), b12 84-5.degree., and also the acetal, b12 101-2.degree.. Twenty-five g. A gave 16.4 g. of the acetal and 5.6 g. of the ester. When A as the trimer was esterified only the ester was obtained. FF yielded a semicarbazone, brilliant needles, m. 135.degree., from alc.; the p-nitrophenylhydrazone, red-brown crystals, m. 80-1.degree., from alc.; the oxime, b14 139.degree., and ethyl naphthocinchoninylpropionate, yellow leaflets, m. 268.degree.. FF with NH2NH2 gave 6-pyridazinone, m. 37.degree., b19 143.degree., sol. in Et2O, CSH6, alc. and AcOEt. FF with MgEtBr gave 3-ethyl-3,6-octanediol (GG), b20 148.degree., m. 41.degree., from petr. ether. GG treated with Ac2O gave 3-ethyl-3,6-octanediol 6-ethanoate (MM), b18, 146-7.degree.. EtO(OH)CH2CH2CHEtOAc. GG when treated with H2SO4 gave 3-ethyl-3,6-octanediol oxide (II), b18 68-9.degree.. This compd. has an odor of camphor. II with MgEtBr did not give a gaseous product but HM did and therefore HM contains an alc. group. 3-Ethyl-3,6-octanediol 3,6-diphenylurethan, white powder, m. 121.degree., was formed when GG was treated with PhNCO during 2 months. Two moles CH2(CO2Et)2 were condensed with FF in the presence of Et2NH (Knovenagel) and the product of the condensation was sapond. 6 hrs. with HCl and the resulting acid was esterified with H2SO4 and alc. Diethyl 3-ethylethanoate-1,6-hexanedioate, EtO2CCH2CH2CH(CH2CO2Et)CH2CO2Et (JJ), b15, 200.degree.. JJ when treated with KOH and then with HCl gave the corresponding triacid (KK), white powder, m. 122.degree.. The anhydride was formed when the triacid was refluxed with AcCl, white cryst. powder, m. 133.degree., insol. in C6H6, C7H8, petr. ether. The monoanilide of KK, a white powder from alc. m. 151.degree.. The mono-p-toluidide, m. 207.degree., white powder. Adipenic acid, HO2C(CH2)2CH:CHCO2H, was formed when A was allowed to stand 4 days with CSHSN and CH2(CO2H)2, white powder, m. 208-10.degree. It decolorizes KMnO4 and absorbs Br. LL when treated with MgEtBr at 0.degree. for 1 hr. gave .alpha.,.alpha.-diethyl-.alpha.'-ethoxytetrahydrofurfuran, b12 69.degree.. It has no action on Schiff's reagent, contains no ethylenic linkage, shown by the use of alk. KMnO4, and it does not react in the cold with KOH. A second product of the action of EtMgBr was 3,6-diethyl-3,6-octanediol, m. 69.degree., b12 154.degree. (Compt. rend. 132, 833) (MM). The phenylurethan m. 187-8.degree., from CSH5. MM was prepd. synthetically by treating EtMgBr with EtBr. MM came from (CH2CO2Et)2 as an impurity in LL. MM yielded with H2SO4 3,6-diethyl-3,6-octanediol oxide, b14 95-6.degree.. 3-Ethyl-3,6-hexanediol (NN), b22 144-5.degree., was prepd. by the action of EtMgBr on butyrolactone formed by the action of KOH on EtO(CHCH2CH2CH2)Cl. NN in Ac2O when warmed 2 hrs. on the steam bath gave 3-ethyl-3,6-hexanediol 6-ethanoate, Et2C(OH)CH2CH2CH2OAc. A diethanoate could not be formed, probably because of steric hindrance. The diphenylurethan of NN m. 106.degree., from alc. and from C6H6. Ethyleuccinic acid aldehyde (OO), OHCCH2CEtCHCO2H, was prepd. by hydrolyzing OHCCH(CO2Et)CH:CH2CO2Et with (CO2H)2 (yield 60%); it decompe. KHCO3, reduces NH3-AgNO3, Fehling soln. and acts on Schiff's reagent. The semicarbazone m. 156.degree., from alc.; the p-nitrophenylhydrazone m. 164.degree., from AcOH; the oxime m. 70.degree., from C6H6 with petr. ether; naphthocinchoninyl-.alpha.-ethylpropionic acid, yellow crystals infusible at 260.degree.; the phenylhydrazide phenylhydrazone, white crystals, m. 175.degree.. OO does not polymerize when esterified with HCl in alc.; the ester obtained, b20 103-4.degree., reacts with Schiff's reagent, NH3-AgNO3, and Fehling soln. It gave a semicarbazone and p-nitrophenylhydrazone. A second product from the esterification was ethoxyethylbutyrolactone, EtCH.CH2.CH(OEt).O.CO, b20 114-5.degree., an isomer of the ester. The introduction of an Et group into A prevents the polymerization of OO and the acetal is not formed. The results agree with those of Blaise and Courtot (Bull. soc. chim. 35, 989) on acid aldehydes.

SO Ann. chim. (1921), 17, 38-132

AB The object of the work was to study a general method for prepg. aldehyde acids, certain of which have been prepd. in small yield by Harries and Tank (C. A. 2, 2375) who decompd. ozonides with H2O (also C. A. 3, 183, and Ann. 343, 359(1905)). These compds. have also been found among the oxidation products of unsatd. acids (Ann. 143, 34(1867); 140, 66(1866); Ber. 34, 1500(1901); Bull. soc. chim. [3] 31, 161(1904); Ber. 33,

2763(1900)). Perkin and Sprankling prepd. HO2C(CH2)2CHO (A) by condensing ClNa(CO2Et)2 with MeCBr(OEt)2 (J. Chem. Soc. 75, 16(1899)). Frankenstein (Diss. Koenigsberg 1899), and von Ungern Sternberg (Diss. Koenigsberg 1904)prepd. A by decompg. aconic acid (B) with H2O. Homologs of A cannot be prepd. by this method because homologs of B are not known. Harries and Alefeld formed A in 10% yield by decompg. the ozonide of allylacetic acid with H2O. OHCCH(CO2Et)CH2CO2Et (F) was prepd. by Wislicenus, Boklen and Reuthe (C. A. 3, 790) by condensing HCO2Et (C) with EtO2CCH:CHCO2Et (D) but C. found that NaOEt gave good results. To 27.6 g. Na as NaOEt was added in small amts., 174 g. D with 89 g. C and after the mixt. stood in the cold for several days. OHCCH(CO2Et)·CNNaCO2Et (E) sepd. It was then treated with H2SO4, extd. with Et2O and the calcd. amt. of F, b15 128-148.degree., was obtained. The range is wide because of the presence of the enolic and aldehyde forms. The Meyer technic was used for the study of the equil. (C. A. 8, 1774). The enolic form in F after standing several hrs. was 50% and in a 4.643% soln. in alc. fell to 12% at the end of 4 days. On distn. the first portion contained 30% of enolic F and the last portion 60%. All fractions at the end of several hrs. contained 50% enolic F and the sepn. could not be effected by distn. Ethyl formylsuccinate semicarbazone (CC), white crystals, m. 126.degree., and the p-nitrophenylhydrazone, yellow crystals, m. 100.degree.. Et benzoylformylsuccinate was prepd. by condensing F with BzCl, b14 208-12.degree. (not in accord with the value given by W., R., and B.), needles m. 58-9.degree.. The action of PhNH2 and certain of its derivs. on F was studied. From the product resulting when F interacted with PhNH2 ethyl anilinoitaconate, yellow crystals, m. 102.degree., was obtained. Ethyl p-toluidinoitaconate (G) was prepd. in a similar manner. G sapond. with alc. KOH gave ethyl 1-p-cresyl-3-carboxylate-5-pyrrolinone (J). MeCSN4N.CH:C(CO2Et).CH2.CO, yellow crystals, m. 123-4.degree.. Ethyl benzylaminoitaconate (H) was prepd. by treating F with PhCH2NH2, white crystals, m. 54.degree., and H when treated with alc. KOH followed by HCl gave ethyl 1-benzylamino-3-carboxylate-5-pyrrolinone, yellow crystals, m. 95.degree.. J when sapond. by NaOH gave a small amt. of p-H2NC6H4Me and when the mixt. was treated with H2SO4, HCO2H and (CH2CO2H)2 were formed. NH2OH.HCl and K2CO3 mixed with F gave ethyl formylsuccinate oxime (K), viscous liquid which on distn. gave ethyl beta.-cyanopropionate (L), b18 114-5.degree.. L sapond. with KOH gave (CH2CO2H)2. Succinic acid aldehyde oxime, HON:CHCH2CH2CO2H, white crystals, m. 155.degree.. K when heated is dehydrated and the H2O resulting from this action sapons. the ester group beta. to the CN group, the CO2H group losing CO2 with formation of L. In prepg. (EtO2C)2CHCNHC6CO2Et (M) Et2CHNHCO2Et was first prepd. by the method of Heil, Volhard and Zelinsky and this was then condensed with ClNa(CO2Et)2. The resulting tri-ester was sapond. by heating it 12 hrs. with HCl. The H2O and HCl were eliminated in vacuo and the residue was heated in an oil bath at 150-60.degree. to transform the carboxyethylsuccinic acid into EtCH(CO2H)CH2CO2H (N), of which a 78% yield was obtained (Ann. 192, 148(1878)). N was esterified to M, using alc. N, when heated with AcCl, gave EtCH.CO.O.CO.CH2 (O), b20 140.degree. (Ann. 291, 121(1896)), which with PhNH2 in C6H6 gave ethyl succinic acid anilide (P), crystals from alc., m. 118.degree.. P heated at 180.degree. during 1.5 hrs. gave ethylsuccinic anil, crystals m. 74.degree.. O heated 6 hrs. with PCl5 gave ethylsuccinyl chloride, EtCH(COCl)CH2COCl, b14 94-5.degree., and when this compd. was treated with PhNH2 in Et2O ethylsuccinic dianilide, crystals, m. 205.degree., was formed. Ethyl formylethylsuccinate (Q) was prepd. by treating HCO2Et and M with NaOEt in Et2O in the cold for 3 days. H2SO4 was then added and Q sepd. and after treatment with K2CO3 and distn. was obtained (68% yield) as an oil, b15 145-70.degree.. The enolic form HOCH:C(CO2Et)CHEtCO2Et and the aldehydic form OHCCH(CO2Et)CHEtCO2Et exist and the equil. between these 2 forms as detd. by the Meyer technic was found to be attained slowly. An initial enol content of 37% fell to 17% in 3 weeks. The derivs. of the aldehydic form were the semicarbazone, white crystals from alc., m. 113.degree. the p-nitrophenylhydrazone, m. 113.degree., from AcH. The derivs. from the enolic form were the phenylurethan and the benzoate (the product reported as the phenylurethan was made by condensing Q with BzCl in ClNaSN, b14 220.degree. (C14H22O6). Abstr). Ethyl 1-phenyl-4-carboxylate-5-ethyl-6-pyridasinone, EtCH.CO.NPh.N:CH.CHCO2Et (R), b15 225-40.degree., crystals from alc., was prepd. by heating Q with PhNHNH2; it was sapond. with NaOH to the free acid, crystals m. 179.degree.. Q with PhNH2 gave a thick liquid, ethyl anilinoethylitaconate, RtO2CCHRCH(:CHNHPh)CO2Et, which when sapond. with alc. KOH followed by HCl treatment gave 1-phenyl-4-ethyl-3-carboxyl-5-pyrrolinone (S), EtCH.CO.NPh.CH:CCO2H, yellow crystals from alc., m. 190.degree. (decompn.). Q interacted with p-MeCSN4NH2 and the resulting ethyl p-toluidinoethylitaconate was sapond. with KOH, yielding 1-p-cresyl-4-ethyl-3-carboxyl-5-pyrrolinone (T), yellow crystals from alc., m. 203.degree.. S gave the corresponding ester when treated with alc. and HCl, crystals from alc., m. 99.degree., and T gave the corresponding ester, m. 104.degree.. The equation for the transformation of F into A is: F + 2H2O = CO2 + alc. +A. A curve showing the rate of hydrolysis of F by (CO2H)2 is given, a max. being reached in 1 hr. The reaction was followed by the amt. of CO2 evolved. The (CO2H)2 was eliminated from the mixt. resulting from the hydrolysis by titration with Ca(OAc)2. The Ca(C2O4) was filtered and the ether ext. distd. in vacuo gave A, b15 142-3.degree. (45% yield) (Harries and Alefeld gave b14 134-6.degree.; C. A. 3, 895). (CH2CO2H)2 was also formed. According to the method of von Ungern Sternburg a 50% yield of A is obtained and the transformation of itaconic acid into B is only to the extent of 60%, whereas the transformation of (CH2CO2H)2 into F is quant. A gives with the Schiff reagent a violet color, NH3AgNO3 is reduced at once in the cold as well as is Fehling soln. The semicarbazone m. 194-5.degree. (decompn.) (H. and A. gave 177-8.degree.). The p-nitrophenylphenylhydrazone m. 180-1.degree. (and not at 175.degree.; C. A. 3, 2154). The oxime, white crystals, m. 102-8.degree.. Naphthocinchoninylpropionic acid was prepd. by dissolving C10H7NH2 in alc. with AcCO2H and A and heating the mixt. 2 hrs., yellow crystals from HCO2H and H2O mixt. A was reduced with Hg-Na to O.CO.CH2.CH2.CH2.O and this lactone with NH2NH2.H2O gave butyrolactone hydrazone, H2NNHC(OH):CH2.CH2.CH2.O, leaves from AcOEt, m. 93.degree.. The calcium salt of A was prepd. and the phenylhydrazone. A with H2SO4 polymerizes to the trimer HOOC(CH2)2CHCH(CH2)2CO2H, m. 167, slightly sol. in Et2O. CH(CH2)2CO2H AcOR, and in Na2CO3 but the aldehydic properties are masked-there is no coloration with the Schiff reagent, no semicarbazone, p-nitrophenylhydrazone, nor oxime could be formed, and the product did not reduce NH2-AgNO3. The bonds forming the cycle are attached to the O atoms. References to this compd. are given. The dimer m. 147.degree. (C. A. 6, 1749). The trimer when distd. gave A and hydroxybutyrolactone oxide, (O.CO.CH2.CH2.CH-)2O. A can exist as hydroxybutyrolactone. Elimination of H2O from this compd. would lead to the oxide. The oxide when treated with semicarbaside gave the semicarbazone of A and when treated with alc.-HCl, OHCCH:CHCO2Et was formed. With NaOH the Na salt of A is formed and when the latter is acidified aldolization results in the formation of butyrolactone aldehyde succinic acid, O.CO.CH2CHZCH(CHO)CH2CO2H, which yields a semicarbazone, white powder, slightly sol. in alc., m. 225.degree.. SOCl2 or PCl5 when

acting on A as the trimer gave chlorobutyrolactone, b15 101.degree., which when distd. loses HCl and when treated with aba. alc. gave ethyl acetalsuccinate, EtO2CCH2CH2CH(OEt)2. C. discusses the relation between B, itaconic acid, F and A and he reproduces the work of Swarts (Bull. acad. roy. Belg. [2] 33, 1873). CH2BrCBr(CO2H).CH2CO2H (AA) was heated at 180.degree. and bromoitaconic acid, m. 190-5.degree., was prepd. This on treatment with H2O gave B, m. 170.degree.. AA when heated with H2O gave B. C. concluded that considering the monohalogenated acids prepd. by Wislicenus, Boklen and Reuthe and by Swarts, the true mono-Cl deriv. was obtained by the former experimenters among the products of the action of PCl5 on F. C. believes that Swarts' product is CH2.CH2.O.CH.CBrCO2H and that Frankenstein's hydroxyitaconic acid (Diss. p. 22-31) is formylsuccinic acid (DD) in the enolic form, HOCH:C(CO2H)CH2CO2H. CC treated in aba. alc. with KOH gave after elimination of alc. and treatment with HCl, N-1 - carbamyl - 3 - acetyl - 5 - pyrazolone, HO2CCH2CH.CH:N.N(CONH2).CO (EE), crystals, m. 185.degree., which result from the loss of a mole of H2O from the semicarbazone of DD. To throw light on the course of the reaction taking place when CC is hydrolysed, C. sapond. MeC:N.NH.CO.NH.CH2CO2Et and prepd. by this means N-1-carbamyl-3-methyl-5-pyrazolone, m. 170.degree., which with FeCl3 gave a violet coloration (Compt. rend. 132, 975(1901)). A was esterified in alc. with HCl during 40 hrs., yielding ethyl aldehydosuccinate (FF), b12 84-5.degree., and also the acetal, b12 101-2.degree.. Twenty-five g. A gave 16.4 g. of the acetal and 5.6 g. of the ester. When A as the trimer was esterified only the ester was obtained. FF yielded a semicarbazone, brilliant needles, m. 135.degree., from alc.; the p-nitrophenylhydrazone, red-brown crystals, m. 80-1.degree., from alc.; the oxime, b14 139.degree., and ethyl naphthocinchoninylpropionate, yellow leaflets, m. 268.degree.. FF with NH2NH2 gave 6-pyridazinone, m. 37.degree., b19 143.degree., sol. in Et2O, CSH6, alc. and AcOEt. FF with MgEtBr gave 3-ethyl-3,6-octanediol (GG), b20 148.degree., m. 41.degree., from petr. ether. GG treated with Ac2O gave 3-ethyl-3,6-octanediol 6-ethanoate (HH), b18, 146-7.degree., Et2O(OH)CH2CH2CHEtOAc. GG when treated with H2SO4 gave 1-ethyl-3,6-octamadiol oxide (II), b18 68-9.degree.. This compd. has an odor of camphor. II with MgEtBr did not give a gaseous product but HH did and therefore HH contains an alc. group. 3-Ethyl-3,6-octanediol 3,6-diphenylurethan, white powder, m. 121.degree., was formed when GG was treated with PhNCO during 2 months. Two moles CH2(CO2Et)2 were condensed with FF in the presence of Et2NH (Knovenagel) and the product of the condensation was sapond. 6 hrs. with HCl and the resulting acid was esterified with H2SO4 and alc. Diethyl 3-ethylethanoate-1,6-hexanedioate, EtO2CCH2CH2CH(CH2CO2Et)CH2CO2Et (JJ), b15, 200.degree.. JJ when treated with KOH and then with HCl gave the corresponding triacid (KK), white powder, m. 122.degree.. The anhydride was formed when the triacid was refluxed with AcCl, white cryst. powder, m. 133.degree., insol. in CSH6, C7H8, petr. ether. The monoanilide of KK, a white powder from alc. m. 151.degree.. The mono-p-toluidide, m. 207.degree., white powder. Adipenic acid, HO2C(CH2)2CH:CHCO2H, was formed when A was allowed to stand 4 days with C5H5N and CH3(CO2H)2, white powder, m. 208-10.degree.. It decolorizes KMnO4 and absorbs Br. LL when treated with MgEtBr at 0.degree. for 1 hr. gave .alpha.,.alpha.-diethyl-.alpha.'-ethoxytetrahydrofurfuran, b12 69.degree.. It has no action on Schiff's reagent, contains no ethylenic linkage, shown by the use of alk. KMnO4, and it does not react in the cold with KOH. A second product of the action of EtMgBr was 3,6-diethyl-3,6-octanediol, m. 69.degree., b12 154.degree. (Compt. rend. 132, 833) (MM). The phenylurethan m. 187-8.degree., from C5H5. MM was prepd. synthetically by treating EtMgBr with EtBr. MM came from (CH2CO2Et)2 as an impurity in LL. MM yielded with H2SO4 3,6-diethyl-3,6-octanediol oxide, b14 95-6.degree.. 3-Ethyl-3,6-hexanediol (NN), b22 144-5.degree., was prepd. by the action of EtMgBr on butyrolactone formed by the action of KOH on EtO2CCH2CH2CH2Cl. NN in Ac2O when warmed 2 hrs. on the steam bath gave 3-ethyl-3,6-hexanediol 6-ethanoate, Et2C(OH)CH2CH2CH2OAc. A diethanoate could not be formed, probably because of steric hindrance. The diphenylurethan of NN m. 106.degree., from alc. and from C6H6. Ethylsuccinic acid aldehyde (OO), OHCCH2CHEtCH2CO2H, was prepd. by hydrolyzing OHCCH(CO2Et)CHEtCO2Et with (CO2H)2 (yield 60%); it decomps. KHCO3, reduces NH3-AgNO3, Fehling soln. and acts on Schiff's reagent. The semicarbazone m. 156.degree., from alc.; the p-nitrophenylhydrazone m. 164.degree., from AcOH; the oxime m. 70.degree., from C6H6 with petr. ether; naphthocinchoninyl-.alpha.-ethylpropionic acid, yellow crystals infusible at 260.degree.; the phenylhydrazide phenylhydrazone, white crystals, m. 175.degree.. OO does not polymerize when esterified with HCl in alc.; the ester obtained, b20 103-4.degree., reacts with Schiff's reagent, NH3-AgNO3, and Fehling soln. It gave a semicarbazone and p-nitrophenylhydrazone. A second product from the esterification was ethoxyethylbutyrolactone, EtCH.CH2.CH(OEt):O.CO, b20 114-5.degree., an isomer of the ester. The introduction of an Et group into A prevents the polymerization of OO and the acetal is not formed. The results agree with those of Blaise and Courtot (Bull. soc. chim. 35, 989) on acid aldehydes.

L10 ANSWER 13 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96049919 EMBASE
DOCUMENT NUMBER: 1996049919
TITLE: NMR determination of the structure of Julibroside J1.
AUTHOR: Ma L.; Tu G.; Chen S.; Zhang K.; Lai L.; Xu X.; Tang Y.
CORPORATE SOURCE: Beijing Institute of Microchemistry,Beijing 100091, China
SOURCE: Carbohydrate Research, (1996) 281/1 (35-46).
ISSN: 0008-6215 CODEN: CRBRAT
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Julibroside J1 is a new triterpenoid saponin which contains one triterpene, two monoterpenes and nine sugar residues. The structure has been determined almost exclusively by high-resolution NMR methods. The 1H and 13C NMR spectra of Julibroside J1 C5D5N have been assigned by homonuclear and heteronuclear correlation experiments, such as COSY, CH-COSY, TOCSY, HMBC, HMQC-COSY, HMQC-TOCSY and NOESY. Anomeric configurations were obtained by combined use of 1J(CH) and 3J(H1,H2) and NOESY data. The particular sugar residues were identified by utilising 3J(HH) values obtained from TOCSY cross-peaks, NOE difference spectra, and several 1D-TOCSY spectra, and three-bond intra-ring cross-peaks from a HMBC spectrum. Linkage assignments were made using the HMBC spectrum, and supplemented by NOE data from the NOESY spectrum. The structure of Julibroside J1 was characterised as 3-O-[.beta.-D-xylopyranosyl-(1 .fwdarw. 2)-.alpha.-L-arabinopyranosyl-(1 .fwdarw. 6)-.beta.-D-glucopyranosyl]-21-O-[(6S)-2-trans-2-hydroxymethyl-6-methyl-6 -O-[4-O-((6S)-2-trans-2,6-dimethyl-6-O-(6-deoxy-.beta.-D-glucopyranosyl)-2 ,7-octadienoyl)-6-deoxy-.beta.-D-glucopyranosyl]-2,7-octadienoyl]-acacic acid 28-O-[.beta.-D-glucopyranosyl-(1 .fwdarw. 3)-[.alpha.-L-arabinofuranosyl-(1 .fwdarw. 4)]-.alpha.-L-rhamnopyranosyl-

(1 .fwdarw. 2)]- beta.-D-glucopyranosyl ester.
SO Carbohydrate Research, (1996) 281/1 (35-46).
ISSN: 0008-6215 CODEN: CRBRAT
AB . . . were obtained by combined use of 1J(CH) and 3J(H1,H2) and NOESY data. The particular sugar residues were identified by utilising 3J(HH) values obtained from TOCSY cross-peaks, NOE difference spectra, and several 1D-TOCSY spectra, and three-bond intra-ring cross-peaks from a HMBC spectrum. **Linkage** assignments were made using the HMBC spectrum, and supplemented by NOE data from the NOESY spectrum. The structure of Julibroside. . .

L10 ANSWER 14 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95224482 EMBASE
DOCUMENT NUMBER: 1995224482
TITLE: Isolation and structural characterization of adhesin polysaccharide receptors.
AUTHOR: Cassels F.J., Van Halbeek H.
CORPORATE SOURCE: Division of Medicine, Department of Gastroenterology, Walter Reed Army Inst. of Research,Washington, DC 20307, United States
SOURCE: Methods in Enzymology, (1995) 253/- (69-91). ISSN: 0076-6879 CODEN: MENZAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The procedure for the purification of the adhesin polysaccharide receptor and its hexasaccharide repeating unit from whole S. oralis ATCC 55229 by chemical enzymatic, and chromatographic techniques has been described. Chemical, chromatographic, and mass spectrometric procedures allow preliminary structural characterization of the hexasaccharide repealing unit and polysaccharide. The structural characterizations of the hexasaccharide and polysaccharide are completed using several 1D and 2D NMR techniques. Identification of the anomeric 1H and 13C signals of the glycosyl residues permits, by virtue of their chemical shifts and coupling constants (3J(HH) and 1J(CH), the determination of the configurations of the glycosidic **linkages**. The HMBC connectivities permit the establishment of the hexasaccharide sequence as Rhap.alpha.(1 .fwdarw. 2) Rhap.alpha.(1 .fwdarw. 3)Galp.alpha.(1 .fwdarw. 3)Galp.beta.(1 .fwdarw. 4)Glcp.beta.(1 .fwdarw. 3)Gal. The 1H NMR chemical shifts of the polysaccharide, as determined by the combination of COSY and TOCSY experiments.
SO Methods in Enzymology, (1995) 253/- (69-91). ISSN: 0076-6879 CODEN: MENZAU
AB . . . the anomeric 1H and 13C signals of the glycosyl residues permits, by virtue of their chemical shifts and coupling constants (3J(HH) and 1J(CH), the determination of the configurations of the glycosidic **linkages**. The HMBC connectivities permit the establishment of the hexasaccharide sequence as Rhap.alpha.(1 .fwdarw. 2) Rhap.alpha.(1 .fwdarw. 3)Galp.alpha.(1 .fwdarw. 3)Galp.beta.(1 .fwdarw. . . .

L10 ANSWER 15 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 83000286 EMBASE
DOCUMENT NUMBER: 1983000286
TITLE: [DNA polymorphism in human populations using southern blots].
[LE POLYMORPHISME DE L'ADN DANS LES POPULATIONS HUMAINES REVELE PAR LA METHODE D'HYBRIDATION APRES TRANSFERT.
AUTHOR: Lucotte G.; Rahuel C.; Gautreau C.; et al.
CORPORATE SOURCE: Lab. Genet. Molec. Biochim. Genet., CNTS, 75015 Paris, France
SOURCE: Revue Francaise de Transfusion et Immuno-Hematologie, (**1982**) 25/3 (279-296). CODEN: RFTIDG
COUNTRY: France
DOCUMENT TYPE: Journal
FILE SEGMENT: 022 Human Genetics
LANGUAGE: French
AB Geneticists interested in human **polymorphism** are primarily concerned with the definition of phenotypes of blood groups and other marker systems. This is followed by identification of the biochemical structures of some of these types. It was in this way that it was discovered that in the case of the ABO, **Hh**, P and other systems these specific structures can not be a primary product of genes as they are glucidic in nature. The direct products of genes should necessarily be glycosyltransferases. These enzymes have indeed been identified and their structure is now slowly unfolded. The subject of this article represents a definite stage in the identification of genetic variation as it is concerned with **polymorphism** of the genetic material itself, including sequences which do not appear to code anything. In this manner fundamental developments in molecular genetics can be expected in the next few years.
SO Revue Francaise de Transfusion et Immuno-Hematologie, (**1982**) 25/3 (279-296). CODEN: RFTIDG
AB Geneticists interested in human **polymorphism** are primarily concerned with the definition of phenotypes of blood groups and other marker systems. This is followed by identification. . . . some of these types. It was in this way that it was discovered that in the case of the ABO, **Hh**, P and other systems these specific structures can not be a primary product of genes as they are glucidic in. . . . The subject of this article represents a definite stage in the identification of genetic variation as it is concerned with **polymorphism** of the genetic material itself, including sequences which do not appear to code anything. In this manner fundamental developments in. . .

L10 ANSWER 16 OF 25 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 77182880 EMBASE
DOCUMENT NUMBER: 1977182880
TITLE: An in vitro model of hybrid resistance to bone marrow grafts.
AUTHOR: Shearer G.M.; Waksal H.; Cudkowicz G.
CORPORATE SOURCE: Immunol. Branch, Nat. Cancer Inst., Bethesda, Md., United States
SOURCE: Transplantation Proceedings, (1976) 8/3 (469-475). CODEN: TRPPA8
DOCUMENT TYPE: Journal
FILE SEGMENT: 026 Immunology, Serology and Transplantation
025 Hematology
LANGUAGE: English
AB Cell mediated cytotoxicity can be induced by a basic mice combination for

in vitro CML reactions from which classical H 2K and H 2D alloantigens and in vivo skin transplant rejections are excluded. These combinations are characterized by strong in vivo reactions against **Hh** 1 incompatible haematopoietic transplants. Positive correlations exist between the rejection of haematopoietic transplants in vivo and F1 antiparental cell mediated cytotoxicity in vitro. These correlations include **polymorphism**, immunologic maturation, antigen induced specific reaction absence, selective (but not specific) reaction inhibition by antisera or agents directed against macrophages. The F1 antiparental cytotoxic system is recommended as an in vitro test preceding bone marrow transplants. (Schmid - Munchen)

SO Transplantation Proceedings, (**1976**) 8/3 (469-475).
CODEN: TRPRA4

AB . . . 2D alloantigens and in vivo skin transplant rejections are excluded. These combinations are characterized by strong in vivo reactions against **Hh** 1 incompatible haematopoietic transplants. Positive correlations exist between the rejection of haematopoietic transplants in vivo and F1 antiparental cell mediated cytotoxicity in vitro. These correlations include **polymorphism**, immunologic maturation, antigen induced specific reaction absence, selective (but not specific) reaction inhibition by antisera or agents directed against macrophages.. . .

L10 ANSWER 17 OF 25 BMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 76044072 EMBASE
DOCUMENT NUMBER: 1976044072
TITLE: Genetic regulation of the structure of blood group specific glycoproteins.
AUTHOR: Watkins W.M.
CORPORATE SOURCE: Lister Inst. Prev. Med., London, United Kingdom
SOURCE: Biochemical Society Symposia, (**1974**) Vol. 40/- (125-146).
CODEN: BSSYAT
DOCUMENT TYPE: Journal
FILE SEGMENT: 022 Human Genetics
025 Hematology
029 Clinical Biochemistry
LANGUAGE: English

AB The blood group specific glycoproteins isolated from ovarian cyst fluids are macromolecules composed of 80-90% carbohydrate and 10-20% amino acids. Detailed understanding of the genetic regulation of the structure of these glycoproteins is confined to the blood group active structures at the non reducing ends of the carbohydrate chains. The genetic endowment of an individual with respect to the ABO, **Hh** and Lele blood group genes, and the Sese secretor genes, determines the nature of these structures. The enzymic products of the A, B, H and Le genes are glycosyltransferases that add specific sugars in a given positional and anomeric **linkage** to the carbohydrate chains in the precursor glycoprotein. The Se gene controls the expression of the H gene in secretory tissues and, since the H active structure is the acceptor for the sugars transferred by the A and B gene specified enzymes, glycoproteins lacking A, B and H activities are isolated from the secretions of individuals homosygous for the allele se. Heterogeneity of carbohydrate chain endings in the blood group active glycoprotein preparations isolated from any one individual appears to be dependent to a large extent on the temporal relationships of the enzymic reactions catalysed by the various blood group gene specified glycosyltransferases.

SO Biochemical Society Symposia, (**1974**) Vol. 40/- (125-146).
CODEN: BSSYAT

AB . . . . at the non reducing ends of the carbohydrate chains. The genetic endowment of an individual with respect to the ABO, **Hh** and Lele blood group genes, and the Sese secretor genes, determines the nature of these structures. The enzymic products of the A, B, H and Le genes are glycosyltransferases that add specific sugars in a given positional and anomeric **linkage** to the carbohydrate chains in the precursor glycoprotein. The Se gene controls the expression of the H gene in secretory. . .

L10 ANSWER 18 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:279034 BIOSIS
DOCUMENT NUMBER: PREV199396009259
TITLE: Determination by heteronuclear NMR spectroscopy of the complete structure of the cell wall polysaccharide of Streptococcus sanguis strain K103.
AUTHOR(S): Reddy, G. Prabhakar; Chang, Chi-Chou; Bush, C. Allen (1)
CORPORATE SOURCE: (1) Dep. Chem. and Biochemistry, University Maryland Baltimore County, Baltimore, MD 21228
SOURCE: Analytical Chemistry, (1993) Vol. 65, No. 7, pp. 913-921. ISSN: 0003-2700.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Although complete structures of complex polysaccharides have traditionally been determined by chemical degradative methods, a number of recent developments in instrumentation have greatly facilitated this task. We illustrate the application of several of these methods in a determination of the complete covalent structure of the polysaccharides from Streptococcus sanguis K103, which is composed of an octasaccharide repeating subunit linked by phosphodiester bonds. Carbohydrate analysis by HPAE-PAD and by reverse-phase chromatography on benzoylated derivatives of the hydrolysis products of the polysaccharide gave glucose (1 mol), galactose (1 mol), rhamnose (2 mol), N-acetylglucosamine (1 mol), and galactose 6-phosphate (1 mol). Circular dichroism of the O-benzoylated monosaccharides showed the absolute configurations to be D for all residues except for rhamnose, which is L. The 1H NMR spectrum was completely assigned by two-dimensional homonuclear methods (DQF-COSY, NOESY, HOHAHA). The stereochemistry of pyranosides was assigned from 3J-HH coupling content values determined from these experiments. The 13C spectrum was assigned by 1H-detected heteronuclear multiple-quantum correlation (1H(13C) HMQC) and by the hybrid method of HMQC-COSY. The glycosidic **linkage** positions of the polymer were determined by 1H-detected multiple-bond correlation (1H(13C) HMBC) and by 2D-NOESY spectra. The position of the phosphodiester **linkage** was determined by splitting observed in the 13C resonances due to 31P couplings leading to the overall structure given in Chart I.

SO Analytical Chemistry, (1993) Vol. 65, No. 7, pp. 913-921.
ISSN: 0003-2700.

AB . . . 1H NMR spectrum was completely assigned by two-dimensional homonuclear methods (DQF-COSY, NOESY, HOHAHA). The stereochemistry of pyranosides was assigned from 3J-HH coupling content values determined from these experiments. The 13C spectrum was assigned by 1H-detected heteronuclear multiple-quantum correlation (1H(13C) HMQC) and by the hybrid method of HMQC-COSY. The glycosidic **linkage** positions of the polymer were determined by 1H-detected multiple-bond

correlation (1H(13C) HMBC) and by 2D-NOESY spectra. The position of the phosphodiester **linkage** was determined by splitting observed in the 13C resonances due to 31P couplings leading to the overall structure given in. . .

L10 ANSWER 19 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:48267 BIOSIS
DOCUMENT NUMBER: BA93:28242
TITLE: A GENETIC POLYMORPHISM IN HEMOGLOBINS OF CHINOOK SALMON ONCORHYNCHUS-TSHAWYTSCHA.
AUTHOR(S): FHYM U S H; WITMLER R E
CORPORATE SOURCE: DEP. FISHERIES AND MARINE BIOL., UNIV. BERGEN, HIGH TECHNOL. CENT., N-5020 BERGEN, NORWAY.
SOURCE: CAN J ZOOL, (1991) 69 (7), 1904-1910.
CODEN: CJZOAG. ISSN: 0008-4301.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB A genetic **polymorphism** with three phenotypes is described for the anodally migrating hemoglobins of adult chinook salmon (Onchorhynchus tshawytscha) from British Columbia, Canada. A genetic model with the genotypes DD, DN, and NN is suggested, on the basis of Hardy-Weinberg genotypic frequencies, in samples of adult chinook salmon from three stocks, and on Mendelian genotypic frequencies among progeny of single-parent crosses. Allelic frequencies differed from stocks. The **polymorphism** may result from a dimorphism in one or both of the tentatively called .beta.-chain loci, with allele D encoding a chain .beta.Pf and allele N encoding a chain .beta.Fs. The two .beta.-loci may be individually regulated. The locus tentatively referred to as .alpha. is monomorphic, as are the minimum of three or four loci that encode the globins of the cathodal hemoglobins. The cathodal and anodal hemoglobins had no globins in common.
SO CAN J ZOOL, (1991) 69 (7), 1904-1910.
CODEN: CJZOAG. ISSN: 0008-4301.
AB A genetic **polymorphism** with three phenotypes is described for the anodally migrating hemoglobins of adult chinook salmon (Onchorhynchus tshawytscha) from British Columbia, Canada. A genetic model with the genotypes DD, DN, and NN is suggested, on the basis of Hardy-Weinberg genotypic frequencies, in samples of adult chinook salmon from three stocks, and on Mendelian genotypic frequencies among progeny of single-parent crosses. Allelic frequencies differed from stocks. The **polymorphism** may result from a dimorphism in one or both of the tentatively called .beta.-chain loci, with allele D encoding a. . .

L10 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:471454 BIOSIS
DOCUMENT NUMBER: BA90:110874
TITLE: STUDIES ON THE BIOCHEMICAL POLYMORPHISM OF BLOOD PROTEIN AND ENZYME IN CHE JU NATIVE HORSES I. GENETIC POLYMORPHISMS OF SERUM PROTEINS.
AUTHOR(S): CHUNG K Y; HAN S K; SHIN Y C; YANG K S
CORPORATE SOURCE: COLL. AGRIC., SANG JI UNIV., KOREAN.
SOURCE: KOREAN J ANIM SCI, (1990) 32 (6), 298-308.
CODEN: HGCHAG. ISSN: 0367-5807.
FILE SEGMENT: BA; OLD
LANGUAGE: Korean
AB By means of starch gel electrophoresis, the biochemical **polymorphism** of .alpha.1-protease inhibitor, albumin, transferin, Xk protein and slow .alpha.2-globulin in a total of 116 Che Ju native horses were examined. The analyzed resulted of phenotype, genotype and gene frequency was following. 1. In the .alpha.1-protease inhibitor(Pi) locus, nine possible phenotypes, except heterozygous FI phenotype, FF, II, LL, SS, FL, FS, IL, IS and LS were identified and assumed to be controlled by four autosomal codominant alleles designated PiF, Pi1, PiL and PiS. The phenotype distribution was estimated to be 68.10% for LL type and 12.93% for IS type and the others were below 10%. The PiL allele with the frequency of 0.741 showed the highest frequency, while the frequencies of Pi1, PiS and PiF alleles with relatively low frequencies were 0.164, 0.078 and 0.017, respectively. 2. With respect to albumin(Al) locus, three different Al phenotypes assumed to be controlled by two codominant alleles were identified as AA, AB and BB and their phenotype distribution was 15.52%, 40.52% and 43.96%, respectively. The frequency of Al$ allele was markedly predominant (0.641) whereas in AlA allele it was 0.358. 3. Concerning transferin(Tf) locus, eleven different phenotypes DD, FF, RR, DF, DO, DR, FH, FO, FR, HR and OR were recognized, assumed to be controlled by five autosomal codominant alleles designated TFD, TfF, TfH, TfO and TfR, but two homozygous type(HH and OO) and two heterozygous type(DH and HO) were not found. The observed percentage of Tf phenotypes FH, FF and RR were found to be 29.31%, 28.45% and 12.93%, respectively, and the other phenotypes were below 10%. Of the total, TfF was the most frequent allele(gene frequency, 0.496), TfR was the second(0.345) and TfD, TfO and TfH were neglible(0.065, 0.60 and 0.034, respectively). 4. As for the Xk protein locus, two different phenotypes FK and KK were observed, whereas homozygous FF type was not recognized. The observed Xk **polymorphism** was assumed to be controlled by a pair of codominant alleles designated XkF and XkK at a single autosomal locus. The number of the KK phenotype was 93.10, that of FK phenotype 6.90%. The significantly higher frequency of XkK allele(0.966) was obtained than that of XkF allele(0.034). 5. In slow .alpha.2-globulin($ .alpha.1) locus, any individual variation was not found, therefore, this locus was defined to be monomorphic.
SO KOREAN J ANIM SCI, (1990) 32 (6), 298-308.
CODEN: HGCHAG. ISSN: 0367-5807.
AB By means of starch gel electrophoresis, the biochemical **polymorphism** of .alpha.1-protease inhibitor, albumin, transferin, Xk protein and slow .alpha.2-globulin in a total of 116 Che Ju native horses were. recognized, assumed to be controlled by five autosomal codominant alleles designated TFD, TfF, TfH, TfO and TfR, but two homozygous type(HH and OO) and two heterozygous type(DH and HO) were not found. The observed percentage of Tf phenotypes FH, FF and. . protein locus, two different phenotypes FK and KK were observed, whereas homozygous FF type was not recognized. The observed Xk **polymorphism** was assumed to be controlled by a pair of codominant alleles designated XkF and XkK at a single autosomal locus.. . .

L10 ANSWER 21 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:223615 BIOSIS
DOCUMENT NUMBER: BA87:115232
TITLE: GENE INTERACTION OF INDUCED INTERMEDIUM MUTATIONS OF TWO-ROW BARLEY III. OVERLAPPING IN DIHYBRID F-2 CLASSIFICATION PATTERNS IN COMBINATIONS OF RECESSIVE INT GENES
AUTHOR(S): LUNDQVIST U; ABEBE B; LUNDQVIST A
CORPORATE SOURCE: SVALOF AB, S-268 00 SVALOV, SWED.

SOURCE: HEREDITAS, (1988) 109 (2), 205-214.
CODEN: HEREAY. ISSN: 0018-0661.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB Totally 56 recessive intermedium mutants, belonging to 8 int loci, have been mutually crossed to one another, and the dihybrid F2 classification patterns have been analysed for deviations from ratios expected for gene combinations where previous analysees have excluded **linkage** as a disturbing factor. A recessive allele "int-x", in the heterozygous state, being able to contribute to the double mutants phenotype for the homozygote "yy" at another int locus, will be revealed by a significant surplus for the "x+y" class balanced against a significant deficit for the "int-y" class. Indications in this respect where shown by the gene constellations **Aa** bb, Aa ff, Aa **hh**, Cc **hh**, Cc kk, Ee aa, Ee **hh**, **Hh** aa, and **Kk** cc. Among these gene constellations, there is a strong tendency, in the doubly homozygous state, to produce spikes of irregular six-rowed or deformed type. It is speculated that the regular six-rowed phenotype has more exacting demands on the gene interaction in the double mutant, demands that cannot generally be fulfilled by a single recessive int allele added to an int homozyote. Different tendencies to bring about phenotypic overlapping among genotypes were indicated not only among different int loci, but also among different alleles within a locus.
SO HEREDITAS, (1988) 109 (2), 205-214.
CODEN: HEREAY. ISSN: 0018-0661.
AB. . . dihybrid F2 classification patterns have been analysed for deviations from ratios expected for gene combinations where previous analysees have excluded **linkage** as a disturbing factor. A recessive allele "int-x", in the heterozygous state, being able to contribute to the double mutants. . . . deficit for the "int-y" class. Indications in this reespect where shown by the gene constellations Aa bb, Aa ff, Aa **hh**, Cc **hh**, Cc kk, Ee aa, Ee **hh**, **Hh** aa, and **Kk** cc. Among these gene constellations, there is a strong tendency, in the doubly homozygous state, to produce spikes of irregular. . . .

L10 ANSWER 22 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:83637 BIOSIS
DOCUMENT NUMBER: BR36:39728
TITLE: HEMOPOIETIC HISTOCOMPATIBILITY **HH**-1 ANTIGEN **POLYMORPHISM** AND MAPPING.
AUTHOR(S): **RIMM**ECKI S M; BENNETT M; KUMAR V; DAVID C S
CORPORATE SOURCE: DEP. PATHOL. AND GRADUATE PROGRAM IN IMMUNOL. UNIV. TEXAS HEALTH SCI. CENT. AT DALLAS, DALLAS, TEXAS 75235.
SOURCE: DAVID, C. S. (ED.). NATO ASI (ADVANCED SCIENCE INSTITUTE) SERIES, SERIES A: LIFE SCIENCES, VOL. 144. H-2 ANTIGENS: GENES, MOLECULES, FUNCTION; MEETING, BAR HARBOR, MAINE, USA, JUNE 5-9, 1987. XVII+849P. PLENUM PRESS: NEW YORK, NEW YORK, USA; LONDON, ENGLAND, UK. ILLUS. (1987) 0 (0), 103-124.
CODEN: NALSDJ. ISBN: 0-306-42804-0.
FILE SEGMENT: BR; OLD
LANGUAGE: English
TI HEMOPOIETIC HISTOCOMPATIBILITY **HH**-1 ANTIGEN **POLYMORPHISM** AND MAPPING.
SO DAVID, C. S. (ED.). NATO ASI (ADVANCED SCIENCE INSTITUTE) SERIES, SERIES A: LIFE SCIENCES, VOL. 144. H-2 ANTIGENS: GENES, MOLECULES, FUNCTION; MEETING, BAR HARBOR, MAINE, USA, JUNE 5-9, 1987. XVII+849P. PLENUM PRESS: NEW YORK, NEW YORK, USA; LONDON, ENGLAND, UK. ILLUS. (1987) 0 (0), 103-124.
CODEN: NALSDJ. ISBN: 0-306-42804-0.

L10 ANSWER 23 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1987:376013 BIOSIS
DOCUMENT NUMBER: BA84:62510
TITLE: DISRUPTIVE SELECTION FOR GENETIC IMPROVEMENT OF UPLAND COTTON.
AUTHOR(S): NARAYANAN S S; SINGH P; SINGH V V; CHAUHAN S K
CORPORATE SOURCE: DIV. OF CROP IMPROVEMENT, CENTRAL INST. FOR COTTON RES., NAGPUR, MAHARASHTRA 400 010.
SOURCE: INDIAN J AGRIC SCI, (1987) 57 (7), 449-452.
CODEN: IJASA3. ISSN: 0019-5022.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB In a 3-year experiment 3 cycles of disruptive mating and selection made from the F2 onward in the progenies of 3 intraspecific hybrids, viz. 'H 4', 'JKHY 1' and 'CICR **HH** 1', with special emphasis on early maturity released vast genetic variability and transgressive segregates for yield/plant, bolls/plant, boll weight, halo length and ginning percentage in upland cotton (Gossypium hirsutum Linn.). The maturity duration decreased by 45, 35 and 20 days from the early-maturing parent of 'H 4', 'JKHY 1' and 'CICR **HH** 1', respectively. The progenies showed broken **linkage** between boll number and boll weight.
SO INDIAN J AGRIC SCI, (1987) 57 (7), 449-452.
CODEN: IJASA3. ISSN: 0019-5022.
AB. . . selection made from the F2 onward in the progenies of 3 intraspecific hybrids, viz. 'H 4', 'JKHY 1' and 'CICR **HH** 1', with special emphasis on early maturity released vast genetic variability and transgressive segregates for yield/plant, bolls/plant, boll weight, halo. . . . maturity duration decreased by 45, 35 and 20 days from the early-maturing parent of 'H 4', 'JKHY 1' and 'CICR **HH** 1', respectively. The progenies showed broken **linkage** between boll number and boll weight.

L10 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1982:313430 BIOSIS
DOCUMENT NUMBER: BA74:85910
TITLE: GENETIC DIVERSITY FOR BLACK RUST AND BROWN RUST RESISTANCE.
AUTHOR(S): KAUSHAL K; GAUR R; JOSHI R; UPADHYAYA Y M
CORPORATE SOURCE: INDIAN AGRICULTURAL RESEARCH INSTITUTE, REGIONAL STATION, INDORE, 45200.
SOURCE: INDIAN J GENET PLANT BREED, (1982) 42 (1), 114-118.
CODEN: IJGBAG. ISSN: 0019-5200.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB For black rust HD 2009 wheat had a pair of dominant complementary factors and 1 recessive factor. In HD 2177 indicated the operation of 1 dominant and 1 recessive factor. In **HH** 2189, again, a pair of dominant complementary factors and 1 recessive factor was observed. Crosses between resistant cultivars indicated diverse but linked factors 2009 and HD 2198. No segregation was found in the cross HD 2009 .times. HD 2189 indicating identical factors or very close **linkage**. For brown rust all the varieties indicated presence of 2 recessive genes. A suppressor was

observed in 'Pissi Local' against genes present in HD 2189. This suppressor was not operative against genes in the other 2 varieties. Segregation for susceptible plants in all 3 crosses between resistant varieties indicated diversity of genes. These were, however, not independent and **linkage** was observed between some of the factors. Again, the resistance to black rust was not independent of brown rust resistance.

SO INDIAN J GENET PLANT BREED, (1982) 42 (1), 114-118.
CODEN: IJGBAG. ISSN: 0019-5200.

AB . . . complementary factors and 1 recessive factor. In HD 2177 indicated the operation of 2 dominant and 1 recessive factor. In HW 2189, again, a pair of dominant complementary factors and 1 recessive factor was observed. Crosses between resistant cultivars indicated diverse. . . . HD 2198. No segregation was found in the cross HD 2009 .times. HD 2189 indicating identical factors or very close **linkage**. For brown rust all the varieties indicated presence of 2 recessive genes. A suppressor was observed in 'Pissi Local' against. . . . for susceptible plants in all 3 crosses between resistant varieties indicated diversity of genes. These were, however, not independent and **linkage** was observed between some of the factors. Again, the resistance to black rust was not independent of brown rust resistance.

L10 ANSWER 25 OF 25 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1978:227337 BIOSIS
DOCUMENT NUMBER: BA66:39834
TITLE: FEATURES GENETICS AND IN-VIVO IMPORTANCE OF LYMPHOCYTE MEDIATED NATURAL CYTO TOXICITY.
AUTHOR(S): PETRANYI G G; GYORFFY G; BENCZUR M; VARGA M; GYODI E; ONODY K; FUST G; LANG I
CORPORATE SOURCE: DEP. TRANSPLANT. IMMUNOL., NAT. INST. HAEMATOL. BLOOD TRANSFUS., BUDAPEST, HUNG.
SOURCE: PANNINERVA MED, (1978) 20 (1), 71-80.
CODEN: PMMDAE. ISSN: 0031-0808.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The mechanism of action and in vivo role of natural killer cells was reviewed. The natural killer cells belong to the O lymphocyte population which usually possess Fc receptors and receptors for the 3rd component at complement. The differences and similarities of the immune, antibody mediated and spontaneous killer mechanisms which can be demonstrated by the effect of metabolite inhibitors and membrane active substances were discussed. Spontaneous killer cells are sensitive to cytostatic drugs but are resistant to total body irradiation. The uropode of the motile spontaneous killer lymphocyte participates in the killer function. Certain specificities are presumable, however, sensitivity of the target cell is also responsible for the degree of this activity. In vivo the spontaneous killer activity may be involved in the resistance to leukemia transplants. The lymphocyte population may be responsible for the Hh system-determined hybrid resistance and allogeneic inhibition mechanism. The spontaneous killer cell activity is under polygenetic control, highly determined by the histocompatibility region linked gene (s). A strong correlation exists between the H-region linked in vivo resistance and the in vivo lymphocyte activity. Genetic studies also indicate a **linkage** between the natural killer activity and Hh-1 system. Human and mouse lymphocytes were studied.

SO PANMINERVA MED, (1978) 20 (1), 71-80.
CODEN: PMMDAE. ISSN: 0031-0808.

AB . . . spontaneous killer activity may be involved in the resistance to leukemia transplants. The lymphocyte population may be responsible for the Hh system-determined hybrid resistance and allogeneic inhibition mechanism. The spontaneous killer cell activity is under polygenetic control, highly determined by the. . . correlation exists between the H-region linked in vivo resistance and the in vivo lymphocyte activity. Genetic studies also indicate a **linkage** between the natural killer activity and Hh-1 system. Human and mouse lymphocytes were studied.

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(FILE 'HOME' ENTERED AT 18:18:24 ON 13 MAR 2002)

FILE 'MEDLINE, CABLUS, EMBASE, BIOSIS' ENTERED AT 18:18:35 ON 13 MAR 2002
L1 1726 S RUDDY D?/AU OR WOLFF R?/AU
L2 1 S L1 AND HEMACHROMATOSIS
L3 37 S L1 AND HE
L4 17 DUP REM L3 (20 DUPLICATES REMOVED)
L5 9272 S HH OR HEMOCHROMOTOSIS
L6 0 S L5 (P) 24DL
L7 0 S L5 (P) 24DL
L8 304 S L5 (P) (LINKAGE OR POLYMORPHISM?)
L9 131 DUP REM L8 (173 DUPLICATES REMOVED)
L10 25 S L9 AND PD<19961523

=> end
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	114.82	114.97

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-13.63	-13.63

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Search Results - Record(s) 1 through 10 of 13 returned.

1. Document ID: US 6228594 B1

L3: Entry 1 of 13 File: USPT May 8, 2001

US-PAT-NO: 6228594
DOCUMENT-IDENTIFIER: US 6228594 B1

TITLE: Method for determining the presence or absence of a hereditary hemochromatosis gene mutation

DATE-ISSUED: May 8, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thomas; Winston J.	San Mateo	CA		
Drayna; Dennis T.	San Mateo	CA		
Feder; John N.	Mountain View	CA		
Gnirke; Andreas	San Carlos	CA		
Ruddy; David	San Francisco	CA		
Tsuchihashi; Zenta	Menlo Park	CA		
Wolff; Roger K.	Belmont	CA		

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 536/23.5, 536/24.31, 536/24.33

CLAIMS:

What is claimed is:

1. A method to determine the presence or absence of a common hereditary hemochromatosis (HH) gene mutation in an individual, comprising:

assessing DNA or RNA from an individual for the presence or absence of HH-associated allele A of a base-pair mutation designated herein 24d1,

wherein, as a result, the absence of the allele indicates the likely absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the likely presence of the HH gene mutation in the genome of the individual.

2. The method of claim 1, further comprising assessing the DNA or RNA from the individual for the presence or absence of HH-associated allele G of a base-pair mutation designated herein 24d2, wherein, as a result, the absence of both alleles indicates the likely absence of the HH gene mutation in the genome of the individual and the presence of one or both alleles the likely presence of the HH gene mutation in the genome of the individual.

3. The method of claim 1, wherein the assessing step is performed by a process which comprises subjecting the DNA or RNA to amplification using oligonucleotide primers flanking the base-pair mutation 24d1(A).

4. The method of claim 3, wherein the assessing step further comprises an oligonucleotide ligation assay.

5. The method of claim 4, wherein the assessing step further comprises providing a housing having a first well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d1A is present in the DNA or RNA and a second well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d1G is present in the DNA or RNA.

6. The method of claim 5, wherein the assessing step further comprises determining whether the individual is homozygous or heterozygous for 24d1A, wherein when the individual is heterozygous for 24d1A a signal will be observed in both the first and second wells upon conducting the oligonucleotide ligation assay and when the individual is homozygous for 24d1A a signal will be observed in the first well upon conducting the oligonucleotide ligation assay.

7. The method of claim 3, wherein the DNA is amplified with oligonucleotide primers of SEQ ID NO:13 and SEQ ID NO:14.

8. The method of claim 7, wherein the assessing step further comprises an oligonucleotide ligation assay.

9. The method of claim 8, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:15, SEQ ID NO:16 and SEQ ID NO:17.

10. The method of claim 3, wherein RNA is amplified with oligonucleotide primers of SEQ ID NO:18 and SEQ ID NO:19.

11. The method of claim 10, wherein the assessing step further comprises an oligonucleotide ligation assay.

12. The method of claim 11, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17.

13. The method of claim 2, wherein the assessing step is performed by a process which comprises subjecting the DNA or RNA to amplification using oligonucleotide primers flanking 24d2(G).

14. The method of claim 13, wherein the assessing step further comprises an oligonucleotide ligation assay.

15. The method of claim 14, wherein the assessing step further comprises providing a housing having a first well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d2G is present in the DNA or RNA and a second well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d2C is present in the DNA or RNA.

16. The method of claim 15, wherein the assessing step further comprises detecting whether the DNA or RNA is homozygous or heterozygous for 24d2G, wherein when the DNA or RNA is heterozygous for 24d2G a signal will be observed in both the first and second wells upon conducting the oligonucleotide ligation assay and when the DNA or RNA is homozygous for 24d2G a signal will be observed in the first well upon conducting the oligonucleotide ligation assay.

17. The method of claim 13, wherein DNA is amplified with oligonucleotide primers of SEQ ID NO:24 and SEQ ID NO:25.

18. The method of claim 17, wherein the assessing step further comprises an oligonucleotide ligation assay.

19. The method of claim 18, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:26, SEQ ID NO:27 and SEQ ID NO:28.

2. Document ID: US 6140305 A

L3: Entry 2 of 13 File: USPT Oct 31, 2000

US-PAT-NO: 6140305
DOCUMENT-IDENTIFIER: US 6140305 A

TITLE: Hereditary hemochromatosis gene products

DATE-ISSUED: October 31, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thomas; Winston J.	San Mateo	CA		
Drayna; Dennis T.	Bethesda	MD		
Feder; John N.	Mountain View	CA		
Gnirke; Andreas	San Carlos	CA		
Ruddy; David	San Francisco	CA		
Tsuchihashi; Zenta	Menlo Park	CA		
Wolff; Roger K.	Mill Valley	CA		

US-CL-CURRENT: 514/2; 530/350

CLAIMS:

What is claimed is:

1. An isolated polypeptide comprising the amino acid sequence as shown in SEQ ID NO:2.

2. An isolated polypeptide comprising the amino acid sequence as shown in SEQ ID NO:4.

3. An isolated polypeptide comprising the amino acid sequence as shown in SEQ ID NO:6.

4. An isolated polypeptide comprising the amino acid sequence as shown in SEQ ID NO:8.

5. An isolated polypeptide comprising an alpha1 domain of a MHC Class I protein contained within the amino acid sequence as shown in SEQ ID NO:2.

6. An isolated polypeptide comprising an alpha2 domain of a MHC Class I protein contained within the amino acid sequence as shown in SEQ ID NO:2.

7. An isolated polypeptide comprising an alpha3 domain of a MHC Class I protein contained within the amino acid sequence as shown in SEQ ID NO:2.

8. An isolated polypeptide comprising a transmembrane domain of a MHC Class I protein contained within the amino acid sequence as shown in SEQ ID NO:2.

9. The isolated polypeptide of claim 1, in which amino acid residue #65 is changed from serine to cysteine.

10. The isolated polypeptide of claim 1, which interacts with .beta.-2-microglobulin.

11. The isolated polypeptide of claim 1, which interacts with the transferrin receptor.

12. The isolated polypeptide of claim 1, 2, 3, 4 or 9 which is membrate-associated.

13. The isolated polypeptide of claim 1, 2, 3, 4 or 9 which is fused with a heterologous polypeptide.

14. The isolated polypeptidc of claim 1, 2, 3, 4 or 9 which is a naturally occurring polypeptide.

15. The isolated polypeptide of claim 1, 2, 3, 4 or 9 which is produced by a recombinant DNA method.

16. The isolated polypeptide of claim 1, 2, 3, 4 or 9 which is produced by a chemical synthetic method.

17. A pharmaceutical composition comprising the isolated polypeptide of

claim 1.

3. Document ID: US 6025130 A

L3: Entry 3 of 13 File: USPT Feb 15, 2000

US-PAT-NO: 6025130
DOCUMENT-IDENTIFIER: US 6025130 A

TITLE: Hereditary hemochromatosis gene

DATE-ISSUED: February 15, 2000

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thomas; Winston J.	San Mateo	CA		
Drayna; Dennis T.	San Mateo	CA		
Feder; John N.	Mountain View	CA		
Gnirke; Andreas	San Carlos	CA		
Ruddy; David	San Francisco	CA		
Tsuchihashi; Zenta	Menlo Park	CA		
Wolff; Roger K.	Belmont	CA		

US-CL-CURRENT: 435/6; 435/91.1, 435/91.2, 536/23.1, 536/23.5, 536/24.31, 536/24.33

CLAIMS:

What is claimed is:

1. An isolated nucleic acid up to 11 kb in length comprising a nucleic acid sequence selected from the group consisting of:

(a) nucleic acid sequences having SEQ ID NO:1;

(b) nucleic acid sequences having SEQ ID NO:3; SEQ ID NO:5, or SEQ ID NO:7;

(c) nucleic acid sequences having SEQ ID NO:9; and

(d) nucleic acid sequences having SEQ ID NO:10, SEQ ID NO:11, or SEQ ID NO:12.

2. The isolated nucleic acid of claim 1, wherein said nucleic acid is cDNA.

3. The nucleic acid of claim 1, wherein the nucleic acid is a nucleic acid sequence

having SEQ ID NO:1.

4. The nucleic acid sequence of claim 1, wherein the nucleic acid is a nucleic acid sequence selected from the group consisting of SEQ ID NO:3, SEQ ID NO:5, and SEQ ID NO:7.

5. The nucleic acid sequence of claim 1, wherein the nucleic acid is a nucleic acid sequence selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, and SEQ ID NO:12.

6. A method for diagnosing a patient as having an increased risk of developing HH disease, comprising:

providing DNA or RNA from the individual; and

assessing the DNA or RNA for the presence or absence of an HH-associated allele A having a base mutation designated herein 24d1 (A) in combination with assessing the DNA or RNA for the HH-associated allele G having a base mutation designated herein 24d2 (G),

wherein, as a result, the absence of the alleles indicates the absence of the HH gene mutation in the genome of the individual and the presence of the alleles indicates the presence of the HH gene mutation in the genome of the individual and an increase risk of developing HH disease.

7. The method of claim 6, wherein the assessing step is performed by a process which comprises subjecting the DNA or RNA to amplification using oligonucleotide primers flanking the base-pair mutation 24d1 (A).

8. The method of claim 7, wherein the assessing step further comprises an oligonucleotide ligation assay.

9. The method of claim 8, wherein the assessing step further comprises providing a housing having a first well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d1A is present in the DNA or RNA and a second well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d1G is present in the DNA or RNA.

10. The method of claim 9, wherein the assessing step further comprises determining whether the individual is homozygous or heterozygous for 24d1A, wherein when the individual is heterozygous for 24d1A a signal will be observed in both the first and second wells upon conducting the oligonucleotide ligation assay and when the individual is homozygous for 24d1A a signal will be observed in the first well upon conducting the oligonucleotide ligation assay.

11. The method of claim 7, wherein DNA is amplified with oligonucleotide primers of SEQ ID NO:13 and SEQ ID NO:14.

12. The method of claim 11, wherein the assessing step further comprises an oligonucleotide ligation assay.

13. The method of claim 12, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17.

14. The method of claim 7, wherein RNA is amplified with oligonucleotide primers of SEQ ID NO:18 and SEQ ID NO:19.

15. The method of claim 14, wherein the assessing step further comprises an oligonucleotide ligation assay.

16. The method of claim 15, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17.

17. The method of claim 6, wherein the assessing step is performed by a process which comprises subjecting the DNA or RNA to amplification using oligonucleotide primers

flanking 24d2 (G).

18. The method of claim 17, wherein the assessing step further comprises an oligonucleotide ligation assay.

19. The method of claim 18, wherein the assessing step further comprises providing a housing having a first well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d2 (G) is present in the DNA or RNA and a second well that is adapted for conducting an oligonucleotide ligation assay and providing a signal when 24d2 (C) is present in the DNA or RNA.

20. The method of claim 19, wherein the assessing step further comprises detecting whether the DNA or RNA is homozygous or heterozygous for 24d2 (G), wherein when the DNA or RNA is heterozygous for 24d2 (G) a signal will be observed in both the first and second wells upon conducting the oligonucleotide ligation assay and when the DNA or RNA is homozygous for 24d2 (G) a signal will be observed in the first well upon conducting the oligonucleotide ligation assay.

21. The method of claim 17, wherein DNA is amplified with oligonucleotide primers of SEQ ID NO:24 and SEQ ID NO:25.

22. The method of claim 21, wherein the assessing step further comprises an oligonucleotide ligation assay.

23. The method of claim 22, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:26, SEQ ID NO:27, and SEQ ID NO:28.

24. An oligonucleotide of at least 8 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

25. The oligonucleotide of claim 24, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

26. An oligonucleotide of at least 9 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

27. The oligonucleotide of claim 26, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

28. An oligonucleotide of at least 10 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7.

29. The oligonucleotide of claim 28, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

30. An oligonucleotide of at least 11 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

31. The oligonucleotide of claim 30, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

32. An oligonucleotide of at least 12 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

33. The oligonucleotide of claim 32, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

34. An oligonucleotide of at least 13 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

35. The oligonucleotide of claim 34, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

36. An oligonucleotide of at least 14 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

37. The oligonucleotide of claim 36, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

38. An oligonucleotide of at least 15 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

39. The oligonucleotide of claim 38, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

40. An oligonucleotide of at least 16 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

41. The oligonucleotide of claim 40, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

42. An oligonucleotide of at least 17 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

43. The oligonucleotide of claim 42, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

44. An oligonucleotide of at least 18 consecutive nucleotides selected from a sequence unique to SEQ ID NO:1, 3, 5, or 7 or the complement of SEQ ID NO:1, 3, 5, or 7.

45. The oligonucleotide of claim 44, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

46. An oligonucleotide of at least 8 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

47. The oligonucleotide of claim 46, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

48. An oligonucleotide of at least 9 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

49. The oligonucleotide of claim 48, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

50. An oligonucleotide of at least 10 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

51. The oligonucleotide of claim 50, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

52. An oligonucleotide of at least 11 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

53. The oligonucleotide of claim 52, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

54. An oligonucleotide of at least 12 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

55. The oligonucleotide of claim 54, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

56. An oligonucleotide of at least 13 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

57. The oligonucleotide of claim 56, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

58. An oligonucleotide of at least 14 consecutive nucleotides selected from a sequence

unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

59. The oligonucleotide of claim 58, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

60. An oligonucleotide of at least 15 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

61. The oligonucleotide of claim 60, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

62. An oligonucleotide of at least 16 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

63. The oligonucleotide of claim 62, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

64. An oligonucleotide of at least 17 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

65. The oligonucleotide of claim 64, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

66. An oligonucleotide of at least 18 consecutive nucleotides selected from a sequence unique to SEQ ID NO:9, 10, 11 or 12 or the complement of SEQ ID NO:9, 10, 11, or 12.

67. The oligonucleotide of claim 66, wherein the oligonucleotide is a member of an oligonucleotide pair for amplification of an HH nucleic acid sequence.

4. Document ID: US 5872237 A

L3: Entry 4 of 13 File: USPT Feb 16, 1999

US-PAT-NO: 5872237
DOCUMENT-IDENTIFIER: US 5872237 A

TITLE: Megabase transcript map: novel sequences and antibodies thereto

DATE-ISSUED: February 16, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Feder; John Nathan	San Carlos	CA		
Kronmal; Gregory Scott	Pacifica	CA		
Lauer; Peter M.	San Francisco	CA		
Ruddy; David A.	San Francisco	CA		
Thomas; Winston	San Mateo	CA		
Tsuchihashi; Zenta	Menlo Park	CA		
Wolff; Roger K.	Mill Valley	CA		

US-CL-CURRENT: 536/23.5

CLAIMS:

What is claimed is:

1. An isolated nucleic acid sequence of approximately 250 kb comprising the sequence of SEQ ID NO:20.

5. Document ID: US 5753438 A

L3: Entry 5 of 13 File: USPT May 19, 1998

US-PAT-NO: 5753438
DOCUMENT-IDENTIFIER: US 5753438 A

TITLE: Method to diagnose hereditary hemochromatosis

DATE-ISSUED: May 19, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Drayna; Dennis T.	San Mateo	CA		
Feder; John N.	Mountain View	CA		
Gnirke; Andreas	San Carlos	CA		
Kimmel; Bruce E.	San Mateo	CA		
Thomas; Winston J.	San Mateo	CA		
Wolff; Roger K.	San Francisco	CA		

US-CL-CURRENT: 435/6; 435/810, 435/91.2, 536/24.33

CLAIMS:

We claim:

1. A method to determine the presence or absence of common hereditary hemochromatosis (HH) in an individual which comprises:

(a) obtaining genomic DNA from said individual;

(b) amplifying a HH-associated allele selected from the group consisting of: HHP-1A, HHP-19G and HHP-29G; and

(c) determining whether said individual is heterozygous or homozygous for a base pair polymorphism in said HH-associated allele, wherein homozygosity for any one or all of said alleles is indicative of HH in the individual and absence of homozygosity for any one or all said alleles is indicative of the absence of HH in the individual.

2. The method of claim 1 which further comprises:

determining the presence or absence of at least one HH-associated microsatellite marker in said individual using a primer pair selected from the group consisting of:

SEQ ID Nos. 1 and 2; SEQ ID NOs. 3 and 4; SEQ ID NOs. 5 and 6; SEQ ID NOs. 7 and 8; SEQ ID NOs. 9 and 10; SEQ ID NOs. 11 and 12; SEQ ID NOs. 13 and 14; SEQ ID NOs. 15 and 16; SEQ ID NOs. 17 and 18; SEQ ID NOs. 19 and 20; SEQ ID NOs. 21 and 22; SEQ ID NOs. 23 and 24; SEQ ID NOs. 25 and 26; SEQ ID NOs. 27 and 28; and SEQ ID NOs. 29 and 30;

wherein the presence of said HH-associated allele in combination with at least one microsatellite marker indicates the likely presence of HH in the individual and

absence of said HH-associated allele and said microsatellite marker indicates the likely absence of HH in the individual.

3. A set of primers for determining the presence or absence of a hereditary hemochromatosis (HH)-associated allele used in an oligonucleotide ligation assay (OLA) selected from the group consisting of:

SEQ ID NOs. 33-35; SEQ ID NOs. 38-40; and SEQ ID NOs. 43-45.

4. A kit for the detection of the presence or absence of an HH-associated allele comprising at least one primer set of claim 3.

5. A method to determine the likelihood of the presence or absence of common hereditary hemochromatosis (HH) in an individual comprising the steps of:

(a) obtaining genomic DNA from said individual;

(b) amplifying a HH-associated microsatellite marker with a primer pair selected from the group consisting of: SEQ ID Nos. 1 and 2; SEQ ID NOs. 3 and 4; SEQ ID NOs. 5 and 6; SEQ ID NOs. 7 and 8; SEQ ID NOs. 9 and 10; SEQ ID NOs. 11 and 12; SEQ ID NOs. 13 and 14; SEQ ID NOs. 15 and 16; SEQ ID NOs. 17 and 18; and SEQ ID NOs. 19 and 20; wherein said amplifying further comprises the optional step of amplifying said DNA with a primer pair selected from the group consisting of: SEQ ID NOs. 21 and 22; SEQ ID NOs. 23 and 24; SEQ ID NOs. 25 and 26; SEQ ID NOs. 27 and 28; and SEQ ID NOs. 29 and 30;

(c) determining the presence or absence of said microsatellite marker, wherein the presence of said microsatellite markers is indicative of the likely presence of HH in the individual and absence of said microsatellite marker is indicative of the likely absence of HH in the individual.

6. The method of claim 5 wherein said method tests at least two of said markers.

7. The method of claim 6 wherein said method tests at least three of said markers.

8. The method of claim 7 wherein said method tests at least four of said markers.

9. The method of claim 5 wherein said genomic DNA is prepared from a sample of blood or buccal swab from said individual.

10. The method of claim 5 which further comprises the amplification of a microsatellite marker using a pair of DNA primers selected from the group consisting of: SEQ ID NOs. 21 and 22; SEQ ID NOs. 23 and 24; SEQ ID NOs. 25 and 26; SEQ ID NOs. 27 and 28; and SEQ ID NOs. 29 and 30.

11. A pair of DNA primers of about 18 nucleotides in length wherein said primer pairs specifically amplify a Common Hereditary Hemochromatosis (HH) associated microsatellite marker selected from the group consisting of: SEQ ID NO. 52; SEQ ID NO. 53; SEQ ID NO. 54; SEQ ID NO. 55; SEQ ID NO. 56; and SEQ ID NO. 57.

12. A DNA primer pair for amplification of a microsatellite marker associated with Common Hereditary Hemochromatosis (HH) wherein the sequences of said primers are selected from the group consisting of: SEQ ID NOs. 7 and 8; SEQ ID NOs. 9 and 10; SEQ ID NOs. 1 and 2; SEQ ID NOs. 3 and 4; SEQ ID NOs. 5 and 6; SEQ ID NOs. 11 and 12; SEQ ID NOs. 13 and 14; SEQ ID NOs. 15 and 16; SEQ ID NOs. 17 and 18; and SEQ ID NOs. 19 and 20.

13. A kit for the detection of the presence or absence of an hereditary hemochromatosis (HH)-associated microsatellite marker in an individual comprising:

(a) at least one pair of DNA primers of about 18 nucleotides in length wherein said primer pairs specifically amplify said (HH)-associated microsatellite marker selected from the group consisting of:

SEQ ID NO 52; SEQ ID NO 53; SEQ ID NO 54; SEQ ID NO 55; SEQ ID NO 56; and SEQ ID NO

57; and optionally

(b) a primer pair selected from the group consisting of: SEQ ID NOs. 7 and 8; SEQ ID NOs. 9 and 10; SEQ ID NOs. 1 and 2; SEQ ID NOs. 3 and 4; SEQ ID NOs. 5 and 6; SEQ ID NOs. 11 and 12; SEQ ID NOs. 13 and 14; SEQ ID NOs. 15 and 16; SEQ ID NOs. 17 and 18; and SEQ ID NOs. 19 and 20.

14. The kit of claim 13 which further comprises a pair of primers selected from the group consisting of: SEQ ID NOs. 21 and 22; SEQ ID NOs. 23 and 24; SEQ ID NOs. 25 and 26; SEQ ID NOs. 27 and 28; and SEQ ID NOs. 29 and 30.

15. A method to identify a potential reduced responsiveness of a subject to interferon treatment for hepatitis C, which method comprises determining the presence or absence of a marker for the common hereditary hemochromatosis gene in said subject according to the method of claim 1, wherein the presence of one of the HH markers indicates a probable reduced responsiveness to said interferon treatment.

16. A method to identify a potential reduced responsiveness of a subject to interferon treatment for hepatitis C, which method comprises determining the presence or absence of a marker for the common hereditary hemochromatosis gene in said subject according to the method of claim 5, wherein the presence of one of the HH markers indicates probable reduced responsiveness to said interferon treatment.

6. Document ID: US 5712098 A

L3: Entry 6 of 13 File: USPT Jan 27, 1998

US-PAT-NO: 5712098
DOCUMENT-IDENTIFIER: US 5712098 A

TITLE: Hereditary hemochromatosis diagnostic markers and diagnostic methods

DATE-ISSUED: January 27, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Tsuchihashi; Zenta	Menlo Park	CA		
Gnirke; Andreas	San Carlos	CA		
Thomas; Winston J.	San Mateo	CA		
Drayna; Dennis T.	San Mateo	CA		
Ruddy; David	San Francisco	CA		
Wolff; Roger K.	Belmont	CA		
Feder; John N.	San Callos	CA		

US-CL-CURRENT: 435/6; 536/23.5, 536/24.3

CLAIMS:

What is claimed is:

1. A method to determine the presence or absence of the common hereditary hemochromatosis (HH) gene mutation in an individual, comprising:

providing DNA or RNA from the individual; and

assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a base pair polymorphism designated herein 24d1,

wherein, as a result, the absence of the allele indicates a likely absence of the HH gene mutation in the genome of the individual and the presence of the allele a likely presence of the HH gene mutation in the genome of the individual.

2. The method of claim 1, wherein the assessing step is performed by a process which comprises subjecting the DNA or RNA to amplification using oligonucleotide primers flanking the base-pair polymorphism 24d1.

3. The method of claim 2, wherein the assessing step further comprises an oligonucleotide ligation assay.

4. The method of claim 3, wherein the assessing step further comprises providing a housing having a first well that is adapted for conducting an oligonucleotide ligation assay and providing a first signal when the A allele of the 24d1 polymorphism is present in the DNA or RNA and a second well that is adapted for conducting an oligonucleotide ligation assay and providing a second signal when the G allele of the 24d1 polymorphism is present in the DNA or KNA.

5. The method of claim 4, wherein the assessing step further comprises detecting whether the DNA or RNA is homozygous or heterozygous for the 24d1 polymorphism, wherein when the DNA or RNA is heterozygous for the 24d1 polymorphism the first and second signal will be observed upon conducting the oligonucleotide ligation assay and when the DNA or RNA is homozygous for the 24d1 polymorphism only the first signal will be observed upon conducting the oligocnucleotide ligation assay.

6. The method of claim 3, wherein DNA is amplified with oligonucleotide primers of SEQ ID NO:5 and SEQ ID NO:6.

7. The method of claim 6, wherein the oligonucleotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9.

8. The method of claim 3, wherein RNA is amplified with oligonucleotide primers of SEQ ID NO: 11 and SEQ ID NO: 12.

9. The method of claim 8, wherein the oligonuceotide ligation assay is accomplished using oligonucleotides of SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:9.

10. A method to evaluate potential responsiveness of an individual infected with hepatitis C to interferon treatment, comprising determining the presence or absence of the common hereditary hemochromatosis gene in the individual according to the method of any one of claims 1-9 wherein the potential responsiveness of an individual infected with hepatitis C is determined.

11. A set of oligonucleotides for an oligonucleotide ligation assay determination of the presence or absence of an HH-associated allele of a base-pair polymorphism, wherein the base pair polymorphism comprises 24d1 and the oligonucleotides comprise the sequences of SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:9.

12. A kit for the detection of the presence or absence of an HH-associated allele of a base-pair polymorphism, the base-pair polymorphism comprising 24d1, as designated herein, the kit comprising the oligonucleotide primer set of SEQ ID NO: 5, 7, 8, 9, 11, 12.

13. The kit of claim 12, further comprising primers for amplifying the DNA containing the base-pair polymorphism designated hrein 24d1.

14. An oligonucleotide primer which is complementary to a DNA sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, and SEQ ID NO:4.

15. A genetic market predictive of a hereditary hemochromatosis (HH) gene mutation comprising a partial sequence of the human genome including at least 16 contiguous nucleotide resiues including "X" in the following nucleotide sequence: ##STR6## and

sequences complementary therewith wherein "X" represents a single base-pair polymorphism of G in a population unaffected with the HH gene mutation and A in a population affected with the HH gene mutation.

16. A genetic marker predictive of a hereditary hemochromatosis (HH) gene mutation comprising a partial sequence of the human genome including at least 16 contiguous nucleotide residues including "X" in the following nucleotide sequence: ##STR7## and sequences complementary therewith wherein "X" represents a single base-pair polymorphism of G in a population unaffected with the HH gene mutation and A in a population affected with the HH gene mutation.

17. Complementary sequences of any one of the sequences of SEQ ID NO: 1 through SEQ ID NO: 13.

7. Document ID: US 5705343 A

L3: Entry 7 of 13 File: USPT Jan 6, 1998

US-PAT-NO: 5705343
DOCUMENT-IDENTIFIER: US 5705343 A

TITLE: Method to diagnose hereditary hemochromatosis

DATE-ISSUED: January 6, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Drayna; Dennis T.	San Mateo	CA		
Feder; John N.	Mount View	CA		
Gnirke; Andreas	San Carlos	CA		
Kimmel; Bruce E.	San Mateo	CA		
Thomas; Winston J.	San Mateo	CA		
Wolff; Roger K.	Belmont	CA		

US-CL-CURRENT: 435/6; 435/810, 435/91.1, 435/91.2, 536/23.1, 536/23.5, 536/24.3, 536/24.31, 536/24.33

CLAIMS:

We claim:

1. A method to determine the likelihood of the presence or absence of common hereditary hemochromatosis (HH) in an individual comprising the steps of:

(a) obtaining genomic DNA from said individual;

(b) amplifying a HH-associated microsatellite marker with a primer pair selected from the group consisting of SEQ ID NOS. 31 and 32; SEQ ID NOS. 33 and 34; SEQ ID NOS. 35 and 36; SEQ ID NOS. 37 and 38; SEQ ID NOS. 39 and 40; SEQ ID NOS. 41 and 42; SEQ ID NOS. 43 and 44; SEQ ID NOS. 45 and 46; SEQ ID NOS.47 and 48; SEQ ID NOS. 49 and 50; SEQ ID NOS. 51 and 52; SEQ ID NOS. 53 and 54; SEQ ID NOS. 55 and 56; SEQ ID NOS. 57 and 58; SEQ ID NOS. 59 and 60; SEQ ID NOS. 61 and 62; SEQ ID NOS. 63 and 64; SEQ ID NOS. 65 and 66; SEQ ID NOS. 67 and 68; SEQ ID NOS. 69 and 70; SEQ ID NOS. 71 and 72;

wherein said amplifying step further comprises the optional step of amplifying said

DNA with a primer pair selected from the group consisting of SEQ ID NOS. 21 and 22; SEQ ID NOS. 23 and 24; SEQ ID NOS. 25 and 26; SEQ ID NOS. 27 and 28; and SEQ ID NOS. 29 and 30; and

(c) determining the presence or absence of said microsatellite marker, wherein the presence of said microsatellite marker is indicative of the likely presence of HH in the individual and absence of said microsatellite marker is indicative of the likely absence of HH in the individual.

2. The method of claim 1 wherein said method tests at least two of said markers.

3. The method of claim 2 wherein said method tests at least three of said markers.

4. The method of claim 3 wherein said method tests at least four of said markers.

5. The method of claim 1 wherein said genomic DNA is prepared from a sample of blood or buccal swab from said individual.

6. A method to identify a potential reduced responsiveness of a subject to interferon treatment for hepatitis C, which method comprises determining the presence or absence of a marker for the common hereditary hemochromatosis in said subject according to the method of claim 1, wherein the presence of one of the HH markers indicates a probable reduced responsiveness to said interferon treatment.

7. The method of claim 1 which further comprises the amplification of a microsatellite marker using a pair of DNA primers selected from the group consisting of SEQ ID NOS. 21 and 22; SEQ ID NOS. 23 and 24; SEQ ID NOS. 25 and 26; SEQ ID NOS. 27 and 28; and SEQ ID NOS. 29 and 30.

8. A method to determine the presence or absence of common hereditary hemochromatosis (HH) in an individual which comprises:

(a) obtaining genomic DNA from said individual;

(b) amplifying a HH-associated allele selected from the group consisting of : HHP-1, HHP-19G, and HHP-29G; and

(c) determining the presence or absence of at least one HH-associated microsatellite marker in said individual using a primer pair selected from the group consisting of SEQ ID NOS. 31 and 32; SEQ ID NOS. 33 and 34; SEQ ID NOS. 35 and 36; SEQ ID NOS. 37 and 38; SEQ ID NOS. 39 and 40; SEQ ID NOS. 41 and 42; SEQ ID NOS. 43 and 44; SEQ ID NOS. 45 and 46; SEQ ID NOS. 47 and 48; SEQ ID NOS. 49 and 50; SEQ ID NOS. 51 and 52; SEQ ID NOS. 53 and 54; SEQ ID NOS. 55 and 56; SEQ ID NOS. 57 and 58; SEQ ID NOS. 59 and 60; SEQ ID NOS. 61 and 62; SEQ ID NOS. 63 and 64; SEQ ID NOS. 65 and 66; SEQ ID NOS. 67 and 68; SEQ ID NOS. 69 and 70; SEQ ID NOS. 71 and 72;

wherein the presence of said HH-associated allele in combination with at least one microsatellite marker indicates the likely presence of HH in the individual and the absence of said HH-associated allele and said microsatellite marker indicates the likely absence of HH in the individual.

9. A method to identify a potential reduced responsiveness of a subject to interferon treatment for hepatitis C, which method comprises determining the presence or absence of a marker for the common hereditary hemochromatosis in said subject according to the method of claim 8, wherein the presence of one of the HH markers indicates a probable reduced responsiveness to said interferon treatment.

10. A pair of primers of about 18 nucleotides in length wherein said primers specifically amplify a common hereditary hemochromatosis (HH) associated marker selected from the group consisting of SEQ ID NO. 85; SEQ ID NO. 86; SEQ ID NO. 87; SEQ ID NO. 88; SEQ ID NO. 89; SEQ ID NO. 90; SEQ ID NO. 91; SEQ ID NO. 92; SEQ ID NO. 93; SEQ ID NO. 94; SEQ ID NO. 95; SEQ ID NO. 96; SEQ ID NO. 97; SEQ ID NO. 98; SEQ ID NO. 99; SEQ ID NO. 100; SEQ ID NO. 101; SEQ ID NO. 102; SEQ ID NO. 103; SEQ ID NO. 104; SEQ ID NO. 105; SEQ ID NO. 106; SEQ ID NO. 107; SEQ ID NO. 108; and SEQ ID NO. 109.

11. A DNA primer pair for amplification of a microsatellite marker associated with common hereditary hemochromatosis (HH) wherein the sequences of said primers are selected from the group consisting of SEQ ID NOS. 31 and 32; SEQ ID NOS. 33 and 34; SEQ ID NOS. 35 and 36; SEQ ID NOS. 37 and 38; SEQ ID NOS. 39 and 40; SEQ ID NOS. 41 and 42; SEQ ID NOS. 43 and 44; SEQ ID NOS. 45 and 46; SEQ ID NOS. 47 and 48; SEQ ID NOS. 49 and 50; SEQ ID NOS. 51 and 52; SEQ ID NOS. 53 and 54; SEQ ID NOS. 55 and 56; SEQ ID NOS. 57 and 58; SEQ ID NOS. 59 and 60; SEQ ID NOS. 61 and 62; SEQ ID NOS. 63 and 64; SEQ ID NOS. 65 and 66; SEQ ID NOS. 67 and 68; SEQ ID NOS. 69 and 70; and SEQ ID NOS. 71 and 72.

12. A kit for detection for the presence or absence of an hereditary hemochromatosis (HH)-associated microsatellite marker in an individual comprising:

(a) at least one pair of primers of about 18 nucleotides in length, wherein said primer pairs specify amplify said (HH)-associated microsatellite marker selected from the group consisting of SEQ ID NO. 85; SEQ ID NO. 86; SEQ ID NO. 87; SEQ ID NO. 88; SEQ ID NO. 89; SEQ ID NO. 90; SEQ ID NO. 91; SEQ ID NO. 92; SEQ ID NO. 93; SEQ ID NO. 94; SEQ ID NO. 95; SEQ ID NO. 96; SEQ ID NO. 97; SEQ ID NO. 98; SEQ ID NO. 99; SEQ ID NO. 100; SEQ ID NO. 101; SEQ ID NO. 102; SEQ ID NO. 103; SEQ ID NO. 104; SEQ ID NO. 105; SEQ ID NO. 106; SEQ ID NO. 107; SEQ ID NO. 108; and SEQ ID NO. 109; and optionally,

a primer pair selected from the group consisting of SEQ ID NOS. 31 and 32; SEQ ID NOS. 33 and 34; SEQ ID NOS. 35 and 36; SEQ ID NOS. 37 and 38; SEQ ID NOS. 39 and 40; SEQ ID NOS. 41 and 42; SEQ ID NOS. 43 and 44; SEQ ID NOS. 45 and 46; SEQ ID NOS. 47 and 48; SEQ ID NOS. 49 and 50; SEQ ID NOS. 51 and 52; SEQ ID NOS. 53 and 54; SEQ ID NOS. 55 and 56; SEQ ID NOS. 57 and 58; SEQ ID NOS. 59 and 60; SEQ ID NOS. 61 and 62; SEQ ID NOS. 63 and 64; SEQ ID NOS. 65 and 66; SEQ ID NOS. 67 and 68; SEQ ID NOS. 69 and 70; and SEQ ID NOS. 71 and 72.

13. The kit of claim 12 which further comprises a pair of primers selected from the group consisting of SEQ ID NOS. 21 and 22; SEQ ID NOS. 23 and 24; SEQ ID NOS. 25 and 26; SEQ ID NOS. 27 and 28; and SEQ ID NOS. 29 and 30.

8. Document ID: US 5872237 A

L3: Entry 8 of 13 File: EPAB Feb 16, 1999

PUB-NO: US005872237A
DOCUMENT-IDENTIFIER: US 5872237 A
TITLE: Megabase transcript map: novel sequences and antibodies thereto

PUBN-DATE: February 16, 1999

INVENTOR-INFORMATION:

NAME	COUNTRY
FEDER, JOHN NATHAN	US
KRONMAL, GREGORY SCOTT	US
LAUER, PETER M	US
RUDDY, DAVID A	US
THOMAS, WINSTON	US
TSUCHIHASHI, ZENTA	US
WOLFF, ROGER K	US

INT-CL (IPC): C07 H 21/04

EUR-CL (EPC): C07K014/47; C07K014/705, C07K014/705 , C12Q001/68

ABSTRACT:

A fine structure map of the 1 megabase region surrounding the candidate HH gene is provided, along with 250 KB of DNA sequence and 8 loci corresponding to candidate genes within the 1 megabase region. These loci are useful as genetic markers for further mapping studies. Additionally, the eight cDNA sequences corresponding to those loci are useful, for example, for the isolation of other genes in putative gene families, and as probes for diagnostic assays. Additionally, the proteins encoded by those cDNAs are useful in the generation of antibodies for analysis of gene expression and in diagnostic assays, and in the purification of related proteins.

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9. Document ID: US 5753438 A

L3: Entry 9 of 13 File: EPAB May 19, 1998

PUB-NO: US005753438A
DOCUMENT-IDENTIFIER: US 5753438 A
TITLE: Method to diagnose hereditary hemochromatosis

PUBN-DATE: May 19, 1998

INVENTOR-INFORMATION:

NAME	COUNTRY
DRAYNA, DENNIS T	US
FEDER, JOHN N	US
GNIRKE, ANDREAS	US
KIMMEL, BRUCE E	US
THOMAS, WINSTON J	US
WOLFF, ROGER K	US

INT-CL (IPC): C12 Q 1/68; C12 P 19/34; C07 H 21/04
EUR-CL (EPC): C12Q001/68

ABSTRACT:

CHG DATE=19990617 STATUS=O>New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes containing this mutation in their genomic DNA.

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10. Document ID: WO 9635802 A1

L3: Entry 10 of 13 File: EPAB Nov 14, 1996

PUB-NO: WO009635802A1
DOCUMENT-IDENTIFIER: WO 9635802 A1
TITLE: METHOD TO DIAGNOSE HEREDITARY HEMOCHROMATOSIS

PUBN-DATE: November 14, 1996

INVENTOR-INFORMATION:

NAME	COUNTRY
DRAYNA, DENNIS T	
FEDER, JOHN N	
GNIRKE, ANDREAS	
KIMMEL, BRUCE E	
THOMAS, WINSTON J	
WOLFF, ROGER K	

INT-CL (IPC): C12 P 19/34; C07 H 21/04; G11 C 11/00; G11 C 15/00; G11 C 17/00

ABSTRACT:

New genetic markers for the presence of a mutation in the common hereditary hemochromatosis (HH) gene are disclosed. The multiplicity of markers permits definition of genotypes characteristic of carriers and homozygotes containing this mutation in their genomic DNA.

Terms	Documents
L1 and HH	13

Search Results - Record(s) 11 through 13 of 13 returned.

11. Document ID: AU 200159917 A, WO 9738137 A1, AU 9726701 A, US 5712098 A, ZA 9706370 A, EP 954602 A1, US 6025130 A, US 6228594 B1, AU 733459 B

L3: Entry 11 of 13 File: DWPI Oct 18, 2001

DERWENT-ACC-NO: 1997-512743
DERWENT-WEEK: 200174

TITLE: Hereditary haemochromatosis gene and variants - useful for diagnosis and treatment of hereditary haemochromatosis disease

INVENTOR: DRAYNA, D T; FEDER, J N ; GNIRKE, A ; RUDDY, D ; THOMAS, W J ; TSUCHIHASHI, Z ; WOLFF, R K

PRIORITY-DATA: 1996US-0652265 (May 23, 1996), 1996US-0630912 (April 4, 1996), 1996US-0632673 (April 16, 1996), 1997ZA-0006370 (July 18, 1997), 2000US-0503444 (February 14, 2000), 2001AU-0059917 (August 16, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200159917 A	October 18, 2001		000	C12N015/12
WO 9738137 A1	October 16, 1997	E	115	C12Q001/68
AU 9726701 A	October 29, 1997		000	C12Q001/68
US 5712098 A	January 27, 1998		018	C12Q001/68
ZA 9706370 A	April 29, 1998		114	A61K000/00
EP 954602 A1	November 10, 1999	E	000	C12Q001/68
US 6025130 A	February 15, 2000		000	C12Q001/68
US 6228594 B1	May 8, 2001		000	C12Q001/68
AU 733459 B	May 17, 2001		000	C12Q001/68

INT-CL (IPC): A61 K 0/00; A61 K 38/00; A61 K 39/00; A61 K 39/395; C07 H 21/04; C07 K 13/00; C07 K 14/00; C12 N 15/00; C12 N 15/12; C12 P 19/34; C12 Q 1/68

ABSTRACTED-PUB-NO: US 5712098A
BASIC-ABSTRACT:

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an

individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

ABSTRACTED-PUB-NO:

US 6025130A
EQUIVALENT-ABSTRACTS:

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for

an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

US 6228594B

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

WO 9738137A

ABSTRACTED-PUB-NO: US 5712098A
EQUIVALENT-ABSTRACTS: A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where,

as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants. USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed). US 6025130A A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants. USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity).

Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed). US 6228594B A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants. USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed). WO 9738137A

CHOSEN-DRAWING: Dwg.0/3 Dwg.0/9

12. Document ID: AU 722885 B, WO 9635803 A1, AU 9658559 A, EP 827550 A1

L3: Entry 12 of 13 File: DWPI Aug 10, 2000

DERWENT-ACC-NO: 1996-518691
DERWENT-WEEK: 200043

TITLE: Diagnosing and genotyping of hereditary haemochromatosis (HH) - using primers to detect specific polymorphisms of the HH gene on chromosome 6p2.1 or novel microsatellite markers

INVENTOR: DRAYNA, D T; FEDER, J N ; GNIRKE, A ; KIMMEL, B E ; THOMAS, W J ; WOLFF, R K

PRIORITY-DATA: 1996US-0599252 (February 9, 1996), 1995US-0436074 (May 8, 1995), 1995US-0559302 (November 15, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 722885 B	August 10, 2000		000	C12P019/34
WO 9635803 A1	November 14, 1996	E	067	C12P019/34
AU 9658559 A	November 29, 1996		000	C12P019/34
EP 827550 A1	March 11, 1998	E	000	C12P019/34

INT-CL (IPC): C07 H 21/04; C12 P 19/34

ABSTRACTED-PUB-NO: WO 9635803A
BASIC-ABSTRACT:

A new method to determine the presence or absence of the common hereditary haemochromatosis (HH) gene mutation in an individual comprises assessing genomic DNA from an individual for the presence or absence of: (a) the HH-associated allele of the base-pair polymorphism HHP-1, HHP-19 or HHP-29; and/or (b) at least one non-optional marker comprising the following microsatellite repeat alleles of group A and opt. of group B: Group A: 19D9(205), 18B4(235), 1A2(239), 1E4(271), 24E2(245), 2B8(206), 3321-1(197), 4073-1(182), 4440-1(180), 4440-2(139), 731-1(177), 5091-1(148), 3216-1(221), 4072-2(148), 950-1(142), 950-2(164), 950-3(165), 950-4(128), 950-5(180), 950-6(151), 950-8(165), 63-1(128), 63-2(169), 63-3(169), 65-1(206), 65-2(81), 373-8(151), 373-29(109), 68-1(167), 241-6(105), 241-29(113) Group B, D62464(206), D6S306(238), D6S258(199), D6S265(122), D6S105(124) and D6S1001(180); where the number in brackets indicates the number of nucleotides between and including the flanking primers and the absence of said genotype indicates the likelihood of the presence of the HH mutation.

USE - The method may be used to diagnose a HH gene mutation. Knowledge of the new genetic markers allows the definition of genotypes characteristic of heterozygous carriers and homozygotes having a HH mutation in their genomic DNA. The potential for HH in an individual interferes with the effectiveness of interferon treatment for hepatitis C infection; by diagnosing this potential, the responsiveness of interferon treatment may be evaluated (claimed).

ABSTRACTED-PUB-NO: WO 9635803A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.0/2

13. Document ID: US 5753438 A, WO 9635802 A1, ZA 9603639 A, AU 9657282 A, US 5705343 A

L3: Entry 13 of 13 File: DWPI May 19, 1998

DERWENT-ACC-NO: 1996-518690
DERWENT-WEEK: 199827

TITLE: Determn. of the common hereditary haemochromatosis gene mutation - using primers based on novel microsatellite repeat flanking sequences or on base-pair polymorphisms HHP-1, HHP-19 or HHP-29

INVENTOR: DRAYNA, D T; FEDER, J N ; GNIRKE, A ; KIMMEL, B E ; THOMAS, W J ; WOLFF, R K

PRIORITY-DATA: 1996US-0599252 (February 9, 1996), 1995US-0436074 (May 8, 1995), 1995US-0559302 (November 15, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5753438 A	May 19, 1998		000	C12Q001/68
WO 9635802 A1	November 14, 1996	E	066	C12P019/34
ZA 9603639 A	January 29, 1997		145	G01N000/00
AU 9657282 A	November 29, 1996		000	C12P019/34
US 5705343 A	January 6, 1998		065	C12Q001/68

INT-CL (IPC): C07 H 21/04; C12 N 15/00; C12 P 19/34; C12 Q 1/68; G01 N 0/00; G11 C 11/00; G11 C 15/00; G11 C 17/00

ABSTRACTED-PUB-NO: US 5705343A
BASIC-ABSTRACT:

A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome.

USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism.

ABSTRACTED-PUB-NO:

US 5753438A
EQUIVALENT-ABSTRACTS:

A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the

opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome.

USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism.

A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome.

USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism.

WO 9635802A

ABSTRACTED-PUB-NO: US 5705343A
EQUIVALENT-ABSTRACTS: A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome. USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism. US 5753438A A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely

presence or absence of the gene mutation in the individual's genome. USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism. WO 9635802A

CHOSEN-DRAWING: Dwg.0/2 Dwg.0/2

Terms	Documents
L1 and HH	13

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Search Results - Record(s) 11 through 13 of 13 returned.

11. Document ID: AU 200159917 A, WO 9738137 A1, AU 9726701 A, US 5712098 A, ZA 9706370 A, EP 954602 A1, US 6025130 A, US 6228594 B1, AU 733459 B

L3: Entry 11 of 13 File: DWPI Oct 18, 2001

DERWENT-ACC-NO: 1997-512743
DERWENT-WEEK: 200174

TITLE: Hereditary haemochromatosis gene and variants - useful for diagnosis and treatment of hereditary haemochromatosis disease

INVENTOR: DRAYNA, D T; FEDER, J N ; GNIRKE, A ; RUDDY, D ; THOMAS, W J ; TSUCHIHASHI, Z ; WOLFF, R K

PRIORITY-DATA: 1996US-0652265 (May 23, 1996), 1996US-0630912 (April 4, 1996), 1996US-0632673 (April 16, 1996), 1997ZA-0006370 (July 18, 1997), 2000US-0503444 (February 14, 2000), 2001AU-0059917 (August 16, 2001)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 200159917 A	October 18, 2001		000	C12N015/12
WO 9738137 A1	October 16, 1997	E	115	C12Q001/68
AU 9726701 A	October 29, 1997		000	C12Q001/68
US 5712098 A	January 27, 1998		018	C12Q001/68
ZA 9706370 A	April 29, 1998		114	A61K000/00
EP 954602 A1	November 10, 1999	E	000	C12Q001/68
US 6025130 A	February 15, 2000		000	C12Q001/68
US 6228594 B1	May 8, 2001		000	C12Q001/68
AU 733459 B	May 17, 2001		000	C12Q001/68

INT-CL (IPC): A61 K 0/00; A61 K 38/00; A61 K 39/00; A61 K 39/395; C07 H 21/04; C07 K 13/00; C07 K 14/00; C12 N 15/00; C12 N 15/12; C12 P 19/34; C12 Q 1/68

ABSTRACTED-PUB-NO: US 5712098A
BASIC-ABSTRACT:

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an

individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

ABSTRACTED-PUB-NO:

US 6025130A
EQUIVALENT-ABSTRACTS:

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for

an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

US 6228594B

A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants.

USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed).

WO 9738137A

ABSTRACTED-PUB-NO: US 5712098A
EQUIVALENT-ABSTRACTS: A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where,

as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants. USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed). US 6025130A A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants. USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity).

Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed). US 6228594B A novel isolated nucleic acid sequence is chosen from: (a) nucleic acid sequences corresponding to a genomic 10825 bp sequence (I) (the hereditary haemochromatosis (HH) gene sequence); (b) nucleic acid sequences corresponding to a cDNA 1437 bp sequence (Ia); (c) nucleic acid sequences corresponding to variants 24d1, 24d2 and 24d7 of (I) and (Ia); Also claimed are: (1) a cloning or expression vector comprising a coding sequence of (I) or (Ia) or a variant as above, and either a replicon operative in a host cell or operably linked with a promoter sequence capable of directing expression of the coding sequence in host cells for the vector; (2) host cells transformed with the vectors as above; (3) a peptide product chosen from the 348 amino acid HH gene product, its variants (24d1, 24d2 and 24d7), or a peptide of at least 56 amino acid residues of these; (4) an antibody produced using a peptide as in (3) as an immunogen; (5) a method to determine the presence or absence of the common HH gene mutation in an individual comprising: (a) providing DNA or RNA from the individual; and (b) assessing the DNA or RNA for the presence or absence of the HH-associated allele A of a 24d1 base pair mutation; where, as a result, the absence of the allele indicates the absence of the HH gene mutation in the genome of the individual and the presence of the allele indicates the presence of the HH gene mutation in the genome of the individual; (6) an animal model for the HH disease, comprising a mammal possessing a mutant or knocked-out HH gene; (7) metal chelation agents, T-cell differentiation factors and therapeutic agents for the mitigation of injury due to oxidative process in vivo or mitigation of iron overload, (comprising a moiety), derived from nucleic acid sequences or peptide products as above; (8) a method for screening potential therapeutic agents for activity in connection with HH disease comprising: (a) providing a screening tool chosen from a cell line, a cell free extract and a mammal containing or expressing a defective HH gene or gene product; (b) contacting the screen tool with the potential therapeutic agent; (c) assaying the screening tool for an activity selected from the group consisting of HH protein folding, iron uptake, transport or metabolism, receptor-like activities, upstream or downstream processes, gene transcription and signalling events; (9) an antisense oligonucleotide directed against a transcriptional product of a nucleic acid sequence as above; and (10) oligonucleotides or pairs of oligonucleotides of at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 nucleotides in length covering a range of nucleotides from (I), (Ia) or their variants. USE - Antibodies directed against the HH gene product can be used to diagnose whether a patient is afflicted with HH disease. The HH gene product can be used to treat a patient diagnosed with HH disease and homozygous for a 24d1 ((A) mutation. Screening mammals for a mutation in the HH gene can be used as a screen for susceptibility to metal toxicities (where a mutation increases susceptibility to the metal toxicity). Screening patients infected with hepatitis virus for a HH gene mutation is used to select patients for alpha -interferon (IFN) treatment, where those patients without a mutation are selected to proceed with alpha -IFN treatment. The oligonucleotides of (10) can be used to detect a polymorphism in the HH gene by amplifying a region of the HH DNA or RNA in a patient sample. (All claimed). WO 9738137A

CHOSEN-DRAWING: Dwg.0/3 Dwg.0/9

12. Document ID: AU 722885 B, WO 9635803 A1, AU 9658559 A, EP 827550 A1

L3: Entry 12 of 13 File: DWPI Aug 10, 2000

DERWENT-ACC-NO: 1996-518691
DERWENT-WEEK: 200043

TITLE: Diagnosing and genotyping of hereditary haemochromatosis (HH) - using primers to detect specific polymorphisms of the HH gene on chromosome 6p2.1 or novel microsatellite markers

INVENTOR: DRAYNA, D T; FEDER, J N ; GNIRKE, A ; KIMMEL, B E ; THOMAS, W J ; WOLFF, R K

PRIORITY-DATA: 1996US-0599252 (February 9, 1996), 1995US-0436074 (May 8, 1995), 1995US-0559302 (November 15, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 722885 B	August 10, 2000		000	C12P019/34
WO 9635803 A1	November 14, 1996	E	067	C12P019/34
AU 9658559 A	November 29, 1996		000	C12P019/34
EP 827550 A1	March 11, 1998	E	000	C12P019/34

INT-CL (IPC): C07 H 21/04; C12 P 19/34

ABSTRACTED-PUB-NO: WO 9635803A
BASIC-ABSTRACT:

A new method to determine the presence or absence of the common hereditary haemochromatosis (HH) gene mutation in an individual comprises assessing genomic DNA from an individual for the presence or absence of: (a) the HH-associated allele of the base-pair polymorphism HHP-1, HHP-19 or HHP-29; and/or (b) at least one non-optional marker comprising the following microsatellite repeat alleles of group A and opt. of group B: Group A: 19D9(205), 18B4(235), 1A2(239), 1E4(271), 24E2(245), 2B8(206), 3321-1(197), 4073-1(182), 4440-1(180), 4440-2(139), 731-1(177), 5091-1(148), 3216-1(221), 4072-2(148), 950-1(142), 950-2(164), 950-3(165), 950-4(128), 950-5(180), 950-6(151), 950-8(165), 63-1(128), 63-2(169), 63-3(169), 65-1(206), 65-2(81), 373-8(151), 373-29(109), 68-1(167), 241-6(105), 241-29(113) Group B, D62464(206), D6S306(238), D6S258(199), D6S265(122), D6S105(124) and D6S1001(180); where the number in brackets indicates the number of nucleotides between and including the flanking primers and the absence of said genotype indicates the likelihood of the presence of the HH mutation.

USE - The method may be used to diagnose a HH gene mutation. Knowledge of the new genetic markers allows the definition of genotypes characteristic of heterozygous carriers and homozygotes having a HH mutation in their genomic DNA. The potential for HH in an individual interferes with the effectiveness of interferon treatment for hepatitis C infection; by diagnosing this potential, the responsiveness of interferon treatment may be evaluated (claimed).

ABSTRACTED-PUB-NO: WO 9635803A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.0/2

13. Document ID: US 5753438 A, WO 9635802 A1, ZA 9603639 A, AU 9657282 A, US 5705343 A

L3: Entry 13 of 13 File: DWPI May 19, 1998

DERWENT-ACC-NO: 1996-518690
DERWENT-WEEK: 199827

TITLE: Determn. of the common hereditary haemochromatosis gene mutation - using primers based on novel microsatellite repeat flanking sequences or on base-pair polymorphisms HHP-1, HHP-19 or HHP-29

INVENTOR: DRAYNA, D T; FEDER, J N ; GNIRKE, A ; KIMMEL, B E ; THOMAS, W J ; WOLFF, R K

PRIORITY-DATA: 1996US-0599252 (February 9, 1996), 1995US-0436074 (May 8, 1995), 1995US-0559302 (November 15, 1995)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5753438 A	May 19, 1998		000	C12Q001/68
WO 9635802 A1	November 14, 1996	E	066	C12P019/34
ZA 9603639 A	January 29, 1997		145	G01N000/00
AU 9657282 A	November 29, 1996		000	C12P019/34
US 5705343 A	January 6, 1998		065	C12Q001/68

INT-CL (IPC): C07 H 21/04; C12 N 15/00; C12 P 19/34; C12 Q 1/68; G01 N 0/00; G11 C 11/00; G11 C 15/00; G11 C 17/00

ABSTRACTED-PUB-NO: US 5705343A
BASIC-ABSTRACT:

A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome.

USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism.

ABSTRACTED-PUB-NO:

US 5753438A
EQUIVALENT-ABSTRACTS:

A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the

opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome.

USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism.

A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome.

USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism.

WO 9635802A

ABSTRACTED-PUB-NO: US 5705343A
EQUIVALENT-ABSTRACTS: A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely presence or absence of the gene mutation in the individual's genome. USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism. US 5753438A A novel method of determining the presence or absence of the common hereditary haemochromatosis (HH) gene mutation comprises assessing the DNA from an individual for the presence or absence of: (a) the HH-associated allele base-pair polymorphism designated HHP-1, HHP-19 or HHP-29; or (b) at least one non-opt. marker selected from the following microsatellite repeat alleles: 19D9:205, 18B4:235, 1A2:239, 1E4:271, 24E2:245, 2B8:206, 3321-1:197, 4073-1:182, 4440-1:180, 4440-2:139, 731-1:177, 5091-1:148, 3216-1:221, 4072-2:148, 950-1:142,950-2 :164, 950-3:165, 950-4:128, 950-5:180, 950-6:151, 950-8:137, 63-1:151, 63-2:113, 63-3:169, 65-1:206, 65-2:81, 373-8:151, 373-29:109, 68-1:167, 241-6:105 and 241-29:113 and opt. the presence of the opt. markers: D6S464:206, D6S306:238, D6S258:199, D6S265:122, D6S105:124 and D6S1001:180 , where the number after the colon is the number of nucleotides between and including the flanking primers, and where presence or absence of the allele indicates likely

presence or absence of the gene mutation in the individual's genome. USE - The method is used to detect for the presence of homozygous HH in related individuals. It has been shown that potential for haemochromatosis interferes with effectiveness of interferon treatment of hepatitis C; knowledge of the HH genotype of a patient can thus be used to design therapeutic protocols for conditions affected by disorders of iron metabolism. WO 9635802A

CHOSEN-DRAWING: Dwg.0/2 Dwg.0/2

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